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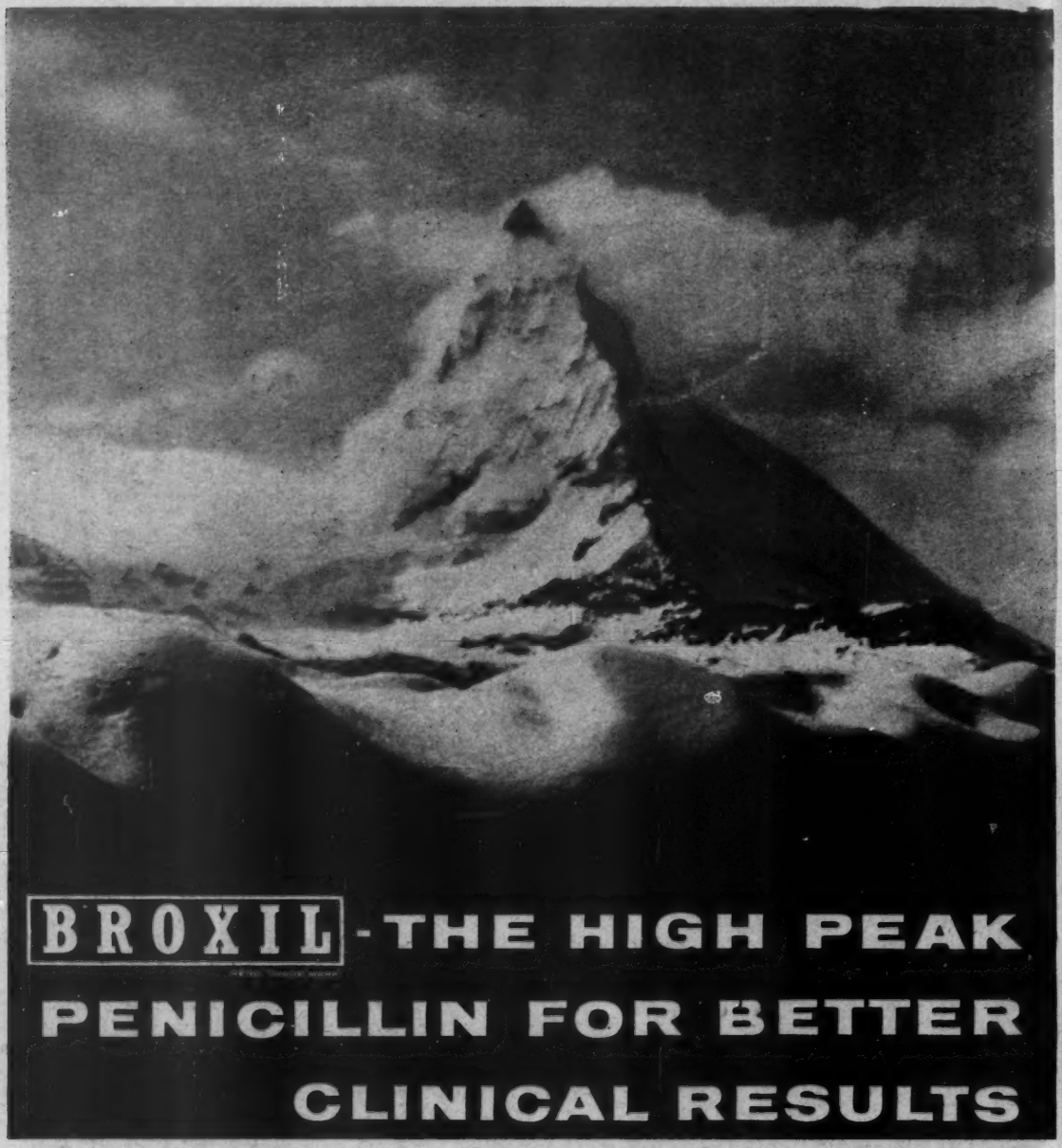

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MYCOBACTERIUM TUBERCULOSIS IN THE AETIOLOGY OF SARCOIDOSIS*

BY

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[WITH SPECIAL PLATE]

In spite of the great interest which has been shown in sarcoidosis in the past 20 years, leading to the recognition of increasing numbers of cases in many parts of the world, controversy concerning its aetiology continues. The validity of a contribution to this controversy depends in large measure upon the definition of sarcoidosis adopted by the person advancing it; for sarcoidosis, like any other disease whose aetiology is not generally agreed, must be so defined that any theory whatever about its aetiology can be discussed intelligibly and with logical propriety (Scadding, 1950, 1956). Any definition which includes the statement, "Sarcoidosis is a disease of unknown aetiology"—for example, that quoted by Ricker and Clark (1949)—is self-stultifying in this respect. An investigator who adheres to such a definition must exclude from the category "sarcoidosis" any case in which a causative agent can be identified, and thus his definition closes his mind to some tenable views concerning aetiology. Important among these is the hypothesis that sarcoidosis may be a reaction to an agent or agents already known, but difficult to demonstrate in this particular manifestation. For if in a given case a probable causative agent has been demonstrated, the definition demands either that the case be excluded from the category "sarcoidosis" or that the presence of this agent be ignored as incidental and unrelated to sarcoidosis. Clearly we must adopt a definition which imposes no *a priori* limitation on our investigation of aetiology.

Definition of Sarcoidosis

Definition of diseases is admittedly difficult. Before we can define an individual disease, we must have a clear definition of the general concept "a disease." I use the term "a disease" to refer to those abnormal phenomena which are common to a group of living organisms with disturbed structure or function, the group being defined in a stated way (Scadding, 1959). The definition of a particular disease must refer to the essential features upon which, in principle (though not necessarily always in practice), it can be decided beyond doubt whether an individual case should be placed in the defined category. These features, which constitute the defining characteristics, may belong to one of several groups, of which the principal can be described in general terms as clinical-descriptive, pathological, and aetiological. The defining characteristics should all belong to one only of these groups, and should be as few as possible and capable of being expressed unequivocally. In sarcoidosis histological features are the essential ones, and therefore they alone should form the basis of the definition. I suggest the following: sarcoidosis is a disease characterized by the presence in all affected organs of epithelioid-cell tubercles without caseation, the older lesions tending to become converted into hyalinized fibrous tissue. An explanatory note may be added to this definition, but not as part of it, that at present the majority of cases conforming to this definition remain of unknown, or at least doubtful, cause. There is a small group associated with exposure to beryllium, which may properly be termed beryllium sarcoidosis. Similarly, if any other cases, either individually or as a group, are found to be associated with a detectable causative agent, it will be permissible to add a term indicative of aetiology to the word "sarcoidosis" to identify them precisely, both by morbid anatomy and by aetiology.

Diagnosis of Sarcoidosis

It can be decided beyond doubt that a case belongs to the category "sarcoidosis" only by a complete necropsy—or by an impossibly large number of biopsies. In practice, in this as in many other diseases, diagnosis is made upon criteria derived from the total description of the disease which results from study of the defined group by all conveniently available methods—clinical, radiological, and immunological—as well as that which forms the basis of the definition. In some instances combinations of clinical features and radiographic changes known to be characteristic of sarcoidosis are sufficient alone to establish a diagnosis with little margin for error. Such combinations of features include symptomless bilateral hilar lymph-node enlargement followed by widespread mottled shadowing in the lungs with spontaneous resolution, and erythema nodosum accompanied by bilateral hilar lymph-node enlargement with low or absent tuberculin sensitivity. These have been shown with sufficient frequency in the past to be associated specifically with non-caseating epithelioid-cell accumulations in the tissues to warrant the diagnosis of sarcoidosis without the need for histological evidence. In some cases showing less characteristic features, biopsy from a single site, even though it shows the typical histological appearance, may be insufficient to establish the diagnosis beyond doubt. In general, it may be said that the need for histological evidence varies inversely with the confidence with which the clinical picture in the individual case is recognized.

In my personally observed series of cases, numbering 230 in all by the end of 1959, histological evidence was obtained from one or more sites in 67%. In the

*Mitchell Lecture delivered at the Royal College of Physicians of London, June 21, 1960.

remainder the diagnosis was made on clinical and radiological grounds. No case with any unusual feature was accepted unless other features were typical and confirmatory histological appearances had been observed from at least one site. It is my purpose here to examine the evidence available from this series of 230 cases concerning the relationship between infection with *Mycobacterium tuberculosis* and sarcoidosis. This, of course, has been one of the most disputed points in the controversy about the cause of sarcoidosis.

Caseating Tuberculosis Following or Preceding Sarcoidosis

Most investigators have agreed that a notably high proportion of those cases of sarcoidosis which reach a chronic stage develop overt tuberculosis, though the reported incidence of this event varies greatly. At one extreme, Riley (1950) reported the development of overt tuberculosis in 13 out of 52 cases of sarcoidosis in negroes in New York, and Ustvedt (1948), reviewing 59 reported necropsies in cases of sarcoidosis, found that tuberculosis was the cause of death in 11; at the other, a few authors have considered that in their series the incidence of overt tuberculosis was no higher than would be expected in the general populations from which their cases were drawn. The development of sarcoidosis after bacteriologically proved tuberculosis has been less frequently recorded, but is nevertheless well documented (Lindig, 1954; Kerbrat and Cellerier, 1954; Refvem, 1954; Emerson and Young, 1956; Lees, 1958; Taylor, 1958).

In my series of 230 cases tubercle bacilli were isolated at some stage in 29, or 13%. In 5 cases they were first found at the time of a change from the clinical picture of sarcoidosis to one of caseating tuberculosis. In 18 cases tubercle bacilli were found without any change being observed in the clinical picture, which remained that associated with sarcoidosis. In the other 6 the bacilli were isolated before the appearance of manifestations of sarcoidosis, at a time when the clinical picture was one of overt tuberculosis—that is, they were examples of sarcoidosis following overt tuberculosis. In 5 additional cases, although no documentary record of the isolation of tubercle bacilli was available, there was an undoubted history of tuberculosis in the past. Thus there were 11 cases in which various overt forms of tuberculosis preceded sarcoidosis, and later I shall consider these 11 cases together.

The separation of the cases in which tubercle bacilli were discovered into these three groups is convenient for purposes of description, but cannot be regarded as precise, for in some cases the transition from a "tuberculous" to a "sarcoid" type of clinical picture was rather indefinite; and some of those which I have placed in the group "sarcoidosis followed by caseating tuberculosis" might possibly have been placed with equal justification in the group "tubercle bacilli found in sarcoidosis." In order to avoid circumlocution I will refer hereafter to the stages of the clinical history in the patients in whom both overt tuberculosis and sarcoidosis were observed as "caseating" and "sarcoid" phases.

Sarcoidosis from which Tubercle Bacilli were Isolated (18 Cases)

The 18 cases in which tubercle bacilli were found in the sarcoid phase merit special attention, since this conflicts most with widely held ideas. The methods by which the bacilli were found are shown in Table I. In one case two cultures proved positive; in the rest the positive cultures were single findings in a series of examinations. No exceptional efforts were made to obtain positive cultures by the examination of large numbers of specimens. In all of 5 cases in which the tubercle bacilli isolated were appropriately examined they were found to be of human strain and normal virulence for the guinea-pig. The bacilli were found at all stages of sarcoidosis (Table II), and at various periods from the apparent onset of the disease (Table III).

The justification for continuing to regard these as cases of sarcoidosis after the finding of tubercle bacilli is that their course and response to treatment remained that usually associated with sarcoidosis. When they were first observed, 17 of them failed to give a skin reaction to 100 tuberculin units (t.u.); 15 of these remained insensitive to tuberculin, and 2 developed moderate reactions to 100 t.u. and 10 t.u. respectively. One reacted to 10 t.u. throughout. The period of observation after the finding of tubercle bacilli varied from 6 months to 8 years, with a mean of 4½ years.

TABLE I.—*Methods by Which M. tuberculosis was Found in 18 Patients with Sarcoidosis Remaining in Sarcoid Phase*

	No. of Cases
Culture of sputum or gastric contents	13
Culture and microscopy	3
Microscopy of sputum during life; culture from lung *post mortem*	1
,, only	4

TABLE II.—*Stage of Pulmonary Sarcoidosis at Time of Isolation of M. tuberculosis in 18 Patients who Remained in Sarcoid Phase, with Their Condition after Periods of Observation Varying from 6 Months to 8 Years (Mean 4½ Years)*

Condition when First Seen	No. of Cases	Present Condition			
		A	B	C	D
Hilar lymph-node enlargement	3	3			
,, ,, + lung infiltration:					
Little or no fibrosis	2	2			
Fibrosis	4			4	
Lung infiltration only:					
Little or no fibrosis	5	1	1	3	
Fibrosis	4			3	1

A=normal chest radiograph; B=abnormal radiograph, no symptoms; C=abnormal radiograph, symptoms; D=dead.

TABLE III.—*Estimated Duration of Sarcoidosis at Time of Isolation of M. tuberculosis in 18 Patients who Remained in Sarcoid Phase*

Years	No. of Cases
½	6
½–2	4
2–5	6
>5	2

No significant response to antituberculosis drugs was observed. Of 17 patients who received such treatment, 4 were not assessable, 2 because the disease was at a stage at which it might be expected to resolve spontaneously and 2 because it was in an irreversible fibrotic stage. Of the remaining 13, 3 showed an apparent slow response and 10 no response, though the quality of the radiographic changes in the lungs suggested potential reversibility. Of this failure to respond to antituberculosis drugs I shall say more later. Corticosteroids were administered to 11 patients, with no response in 3; temporary suppression, followed by relapse on withdrawal of the hormone and later spontaneous partial or complete resolution, in 3; and suppression of symptoms and signs on prolonged treatment in 5, moderate in 3 and slight in 2. Both these results are in accord with experience, both my own and that of others, in the general run of cases of sarcoidosis. The present state in relation to the condition at first

observation of the 18 patients in whom tubercle bacilli were found in the sarcoid phase is shown in Table II. This also is entirely comparable with the course of the disease in the rest of my 230 cases.

Thus, in 18 (8%) of 230 cases of sarcoidosis, tubercle bacilli were found without the clinical course, response to treatment, or prognosis deviating in any way from that observed in the rest of the series, and without the appearance of any other evidence of caseating tuberculosis. Three possible explanations for this can be advanced: (1) that in some cases at least sarcoidosis is an unusual reaction to a tuberculous infection; (2) that patients with sarcoidosis due to some unknown cause are liable to superinfection with tubercle bacilli, but that the manifestations of such infection may be so modified that they are both undetectable clinically and do not affect the course of the patient's illness; and (3) that the findings were the result of errors in or on the way to the laboratory. I shall discuss the first two possibilities later. With regard to the third, though of course error is always possible, I know of no group of cases in which I have received erroneous reports of the finding of tubercle bacilli in such a high proportion as 8%; and while I might be prepared to explain an unexpected finding in a much smaller proportion of cases on this basis, I do not think it reasonable to do so in relation to an observation made with such frequency.

Tuberculosis Preceding Sarcoidosis (11 Cases)

I will now turn to the 11 patients in whom overt tuberculosis preceded sarcoidosis. As already indicated, there was a record of the isolation of tubercle bacilli in the caseating phase in 6 of these. The types of tuberculosis are summarized in Table IV. Tuberculin sensitivity was recorded in only one of them in the caseating phase, when there was a positive reaction to 10 t.u., changing in the sarcoid phase to a negative reaction to 100 t.u. In the sarcoid phase 7 (64%) of these 11 patients did not react to 100 t.u., 3 (27%) reacted to 100 t.u., and one (9%) to 10 t.u. This is very similar to the distribution of reactions to graded doses of tuberculin in my total series of 230 cases (Table V), in which 64% did not react to 100 t.u., 21% reacted to 100 t.u., 11% to 10 t.u., and 4% to 1 t.u.

TABLE IV.—*Types of Caseating Tuberculosis which Preceded Sarcoidosis in 11 Patients*

	No. of Patients	No. in which Isolation of T.B. was Recorded
Primary complex	1	1
Pulmonary	6	2
Cervical adenitis	1	1
Abscess of chest wall	2	2
Peritonitis	1	

TABLE V.—*Sensitivity to Graded Intradermal Doses of Tuberculin in 230 Cases of Sarcoidosis. Percentages Given are Related to the Number with Complete Records*

	No. of Cases
Total number of cases	230
Record incomplete (stated to be "negative")	9
,, complete	221
Negative to 100 t.u.	141 (64%)
Positive ,, 100 ,,	47 (21%)
,, ,, 10 ,,	25 (11%)
,, ,, 1 ,,	8 (4%)

In 7 of the 11 patients an interval ranging from 18 months to 27 years elapsed between the caseating and the sarcoid phases; in 4 there was no such interval, and the sarcoid phase developed imperceptibly from the initial caseating phase. I will quote cases with and without an interval.

Case 1

In 1945 a man, then aged 22, had tuberculous adenitis in the left side of his neck; this softened and was aspirated, tubercle bacilli being cultured from the pus. Towards the end of 1949 he developed a generalized enlargement of lymph-nodes, affecting cervical, axillary, and inguinal groups; a node removed for biopsy showed non-caseating epithelioid-cell tubercles. The spleen was easily palpable. In January, 1950, he developed iridocyclitis in the right eye. A chest radiograph showed bilateral hilar lymph-node enlargement, with diffuse fine mottling mainly in the middle zones of both lungs. A tuberculin test gave a moderate reaction to 100 t.u. Over the next six months all these manifestations gradually subsided, so that by March, 1951, the lymph-nodes and the spleen were no longer palpable, the eye was free from inflammatory changes, and the chest radiograph was clear. He remained quite well until early in 1955, when a lymph-node swelling appeared again in the left side of the neck. The skin now reacted to 10 t.u. with an area of induration 20 × 20 mm. He was treated with isoniazid and *p*-aminosalicylic acid (P.A.S.). The lymph-node softened and sterile pus was aspirated from it; after this the adenitis subsided completely, and the patient has remained well since. Culture of the pus failed to grow tubercle bacilli, but the specimen was taken after 18 months' antibacterial treatment.

In this case there was a change from a caseating to a sarcoid and back again to a caseating phase.

The next case illustrates the group of 4 in which the sarcoid phase developed insidiously from the caseating phase.

Case 2

A woman, born in 1931, was observed at a chest clinic from 1949 to 1953 as a contact of her husband, who had been found in 1949 to be suffering from pulmonary tuberculosis. Her chest radiograph remained clear during this time, but their son, born in 1950, was found to have skin sensitivity to tuberculin at the age of 1 year. She was first seen at the Brompton Hospital in January, 1956, because a small area of faint mottling had been found in the upper zone of the right lung in a chest radiograph (Special Plate, Fig. 1). Sputum examined at this time produced tubercle bacilli on culture. In May, 1956, she was admitted to hospital. Her skin reacted to 10 t.u. Tubercle bacilli were again found on culture, this time from a gastric-lavage specimen. Treatment with isoniazid and P.A.S. was started, but the lung shadows slowly and steadily spread (Special Plate, Fig. 2). She was readmitted in May, 1958. The skin now failed to react even to 1,000 t.u. Liver biopsy showed non-caseating tubercles (Special Plate, Fig. 3). Prednisolone was added to the antituberculosis drugs in June, 1958, and resulted in rapid clearing of the radiographic shadows. However, after the prednisolone was gradually withdrawn and stopped in July, 1959, she started to feel tired, and in October, 1959, a radiograph showed some recurrence of the abnormal shadows.

In this case the sequence of events is striking; there was a steady and uninterrupted progression from exposure to tuberculous infection, through the development of a localized lung lesion with tuberculin sensitivity and tubercle bacilli in the sputum, to a state typical of sarcoidosis, clinically, histologically, and in response to treatment.

Caseating Tuberculosis Following Sarcoidosis (5 Cases)

Turning now to the 5 cases in which the transition from sarcoidosis to caseating tuberculosis was observed, I must emphasize once again the absence of an absolute distinction between them and the group of 18 which I have classed as "sarcoidosis in which tubercle bacilli

were found." Though in 3 of them the transition was marked by an obvious clinical change, in 2 the change was less definite. Specifically "sarcoid" features which disappeared at the transition included skin lesions in 2 and a generalized adenopathy with scattered lung shadows in one. In 2 of them an iritis of sarcoid type had resolved earlier. In all 5 cases the skin had failed to react to 100 t.u. in the sarcoid phase, and reacted to 10 t.u. or 1 t.u. in the caseating phase. The duration of sarcoidosis at the transition ranged from 2 to 12 years. One patient, observed before chemotherapy for tuberculosis was available, died with progressive disease and right ventricular failure; the other 4 received prolonged treatment with antibacterial drugs, with apparent cure of active tuberculosis, but more or less residual fibrosis in the lungs.

Case 3 is typical of those in which there was a sharp transition from the sarcoid to the caseating phase.

Case 3

In 1946 a man, then aged 33, noticed breathlessness on exertion and cough, and one episode of pain in the right side of the chest. A radiograph (Special Plate, Fig. 4) then showed widespread fine mottling in the lungs with a localized opacity in the region of the right middle lobe. In July, 1948, lymph-nodes on both sides of the neck enlarged, and biopsy showed many non-caseating epithelioid-cell tubercles. In June, 1949, he was admitted to hospital for investigation. At this time he was breathless on moderate exertion, and lymph-nodes were easily palpable in the neck, axillae, and groins. The shadowing in the chest radiograph had become much denser, still affecting the right lung more than the left (Special Plate, Fig. 5). Tomography showed evidence of air-containing spaces in the densely affected middle zones of the lungs. Biopsy of a lymph-node again showed many discrete epithelioid-cell tubercles, with some areas of hyaline fibrosis. The skin failed to react to 1,000 t.u. Specimens of sputum were taken for culture at this time. When he was seen as an out-patient in September, 1949, several important events had occurred. A report was received that *M. tuberculosis* had been cultured from the sputum taken when the skin had failed to react to tuberculin; a painful swelling over the left tibia had appeared, and was shown to be a cold abscess associated with an area of rarefaction in the tibia, from which *M. tuberculosis* was later cultured. The skin now reacted briskly to 10 t.u.; there was considerable clearing of the scattered mottling in the lungs (Special Plate, Fig. 6), though the more localized shadows suggestive of fibrosis persisted; and the vital capacity had increased by 1 litre. Tubercle bacilli were now discoverable in the sputum in moderate numbers on microscopy. He was treated for six months with streptomycin and P.A.S., with disappearance of the tubercle bacilli from the sputum and subsidence of the cold abscess. He suffered a minor relapse of the tuberculosis in 1957, with reappearance of tubercle bacilli in the sputum. This has been satisfactorily dealt with by two years of treatment with isoniazid and P.A.S., but he is now left with permanent lung damage causing considerable respiratory disability.

I will now give an example of a gradual transition from a sarcoid to a caseating phase.

Case 4

A woman born in 1920. During her first pregnancy in 1948 she became breathless on exertion. In October, 1950, a chest radiograph showed enlargement of hilar lymph-nodes and some scattered opacities in the lungs (Special Plate, Fig. 7). When I saw her in February, 1952, she easily became breathless on exertion; there were palpable lymph-nodes above both clavicles, and the scar of a minor abrasion of the left shin nearly three years previously was red with a raised nodular rim around a flat atrophic centre. Biopsy of this scar showed the typical histology of sarcoidosis (Special Plate, Fig. 8). A chest radiograph showed denser mottling in the upper zone of the right and middle zone of the left lung and persistently enlarged hilar lymph-nodes (Special Plate, Fig. 9). The skin failed to react to 1,000 t.u. Temporary remission of symptoms and clearing of the skin lesion followed the administration of cortisone for three weeks, but was not maintained when this was withdrawn. B.C.G. vaccination later in 1952 caused a local nodule, which developed and disappeared within nine days, and after this the skin gave a small reaction to 100 t.u. Over the next two years she slowly improved without treatment, but in April, 1955, she had a febrile illness accompanied by a localized shadow in the middle zone of the left lung. She was treated with streptomycin and isoniazid for a short time and improved. In December, 1955, she had another febrile attack, with little change in radiographic appearance, but the skin now reacted to 10 t.u., and one sputum specimen out of three grew human-type tubercle bacilli on culture. After this, efforts were made to maintain prolonged treatment with antituberculosis drugs. Though no further isolation of tubercle bacilli has been recorded, the progress of the disease from this time onwards is compatible with caseating tuberculosis. The shadow in the middle zone of the left lung resolved; new shadows appeared in the right lung in October, 1957, and in the left lung in January, 1958, and resolved; calcification gradually developed at both hila and in the right lung; and stenosis of the anterior segmental bronchus of the right upper lobe, apparently in association with the lymph-node calcification, has been confirmed bronchographically. This stenosis was complicated by transient abscess-formation in the obstructed segment in October, 1958 (Special Plate, Fig. 10). In October, 1959, she was well, with only slight dyspnoea on exertion; radiographically there was evidence of atelectasis of the obstructed segment of the right upper lobe, extensive calcification at the hila, especially the left, but little residual abnormality in the lung fields.

Calcification Developing in the Late Stage of Pulmonary Sarcoidosis

In several other cases I have observed calcification of the type usually associated with caseous residues of pulmonary tuberculosis developing in patients whose cases otherwise conformed to all accepted concepts of sarcoidosis. These I have perhaps arbitrarily regarded as remaining in the sarcoid phase.

Case 5

A farmer, then aged 41, was first seen by me in November, 1950. He had been becoming gradually more breathless on exertion for four years. Examination revealed moderate enlargement of the liver and considerable enlargement of the spleen. The chest radiograph (Special Plate, Fig. 11) showed coarse mottling throughout both lungs. The skin failed to react to 1,000 t.u. Biopsy of an axillary lymph-node showed many non-caseating tubercles. There was no response to three months' treatment with streptomycin and P.A.S.; but immediate diminution in the size of the liver and spleen, considerable subjective improvement, and slight resolution of the lung shadows were observed during three weeks' administration of cortisone, 100 mg. daily, in July, 1951. This improvement was partially maintained after cessation of treatment, the liver and spleen not returning to their former size. Over the years these organs have become impalpable. The mottled shadowing in the chest radiograph has gradually given place to an irregular linear pattern suggestive of fibrosis and emphysema; and calcification has appeared at the apex of the right lung and at both hila, first becoming evident in September, 1952. By April, 1960, it was very obvious, and of a type normally associated with healed pulmonary tuberculosis (Special Plate, Fig. 12).

Tuberculosis with Low Tuberculin Sensitivity and Poor Response to Chemotherapy

Just as the separation of those of my cases of sarcoidosis in which tubercle bacilli were isolated into

FIG. 1.—Case 2. Radiograph of upper zone of right lung, January, 1956, showing localized tuberculosis.

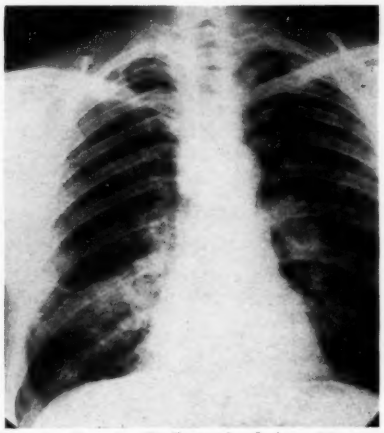

FIG. 4.—Case 3. Radiograph of chest, November, 1946.

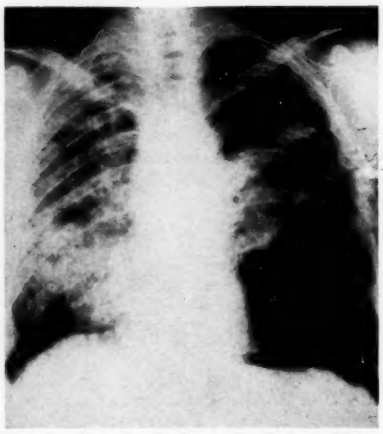

FIG. 5.—Case 3. Radiograph of chest, May, 1949.

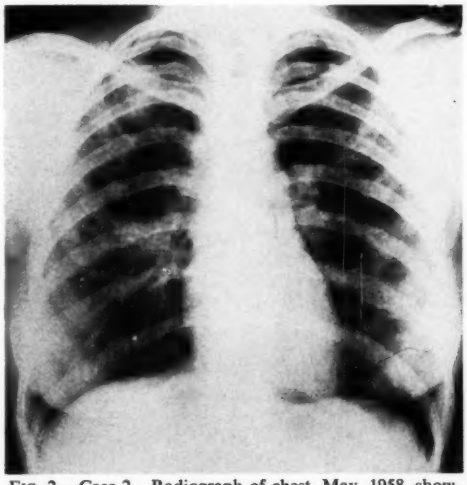

FIG. 2.—Case 2. Radiograph of chest, May, 1958, showing spread of mottled shadowing in both lungs during antituberculosis chemotherapy.

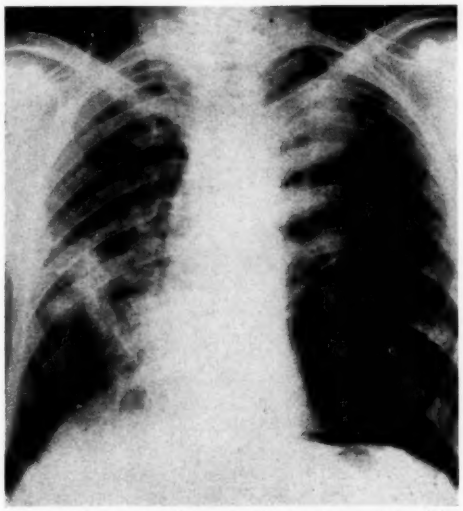

FIG. 6.—Case 3. Radiograph of chest, November, 1949, showing clearing of mottled shadows at time of appearance of tuberculin sensitivity and of tubercle bacilli in sputum.

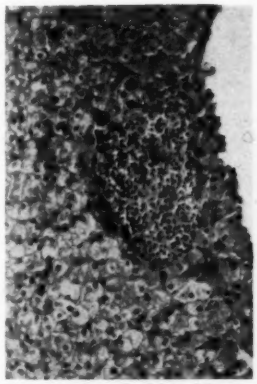

FIG. 3.—Case 2. Liver biopsy, May, 1958. (H. and E. ×188.)

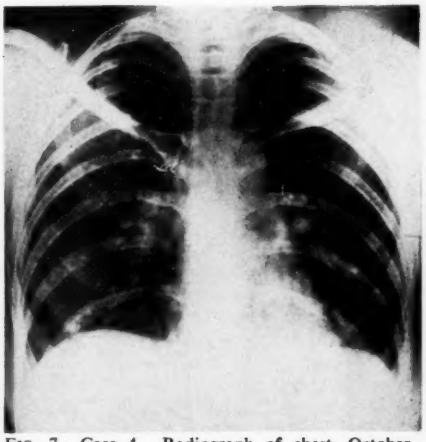

FIG. 7.—Case 4. Radiograph of chest, October, 1950.

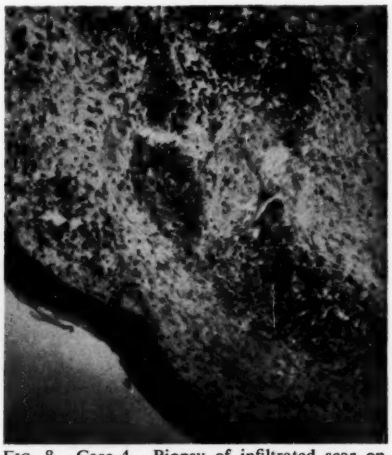

FIG. 8.—Case 4. Biopsy of infiltrated scar on left shin, February, 1952. (H. and E. ×168.)

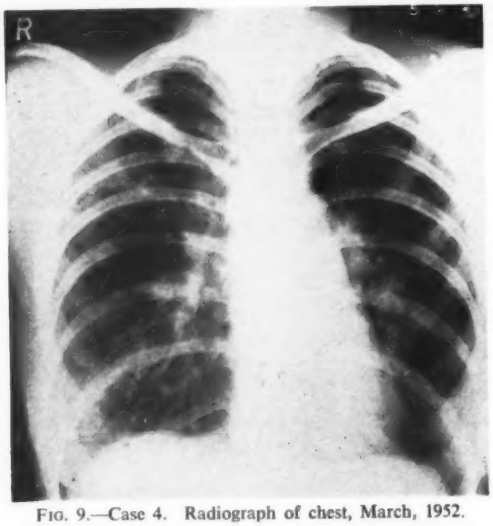

FIG. 9.—Case 4. Radiograph of chest, March, 1952.

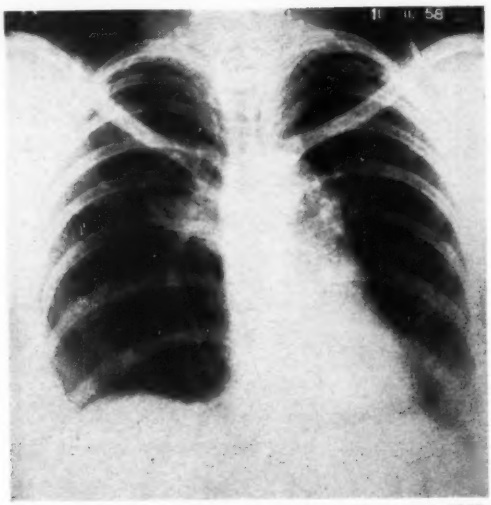

FIG. 10.—Case 4. Radiograph of chest, November, 1958.

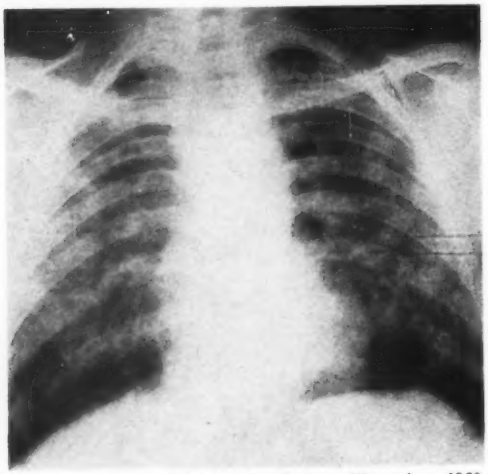

FIG. 11.—Case 5. Radiograph of chest, November, 1950.

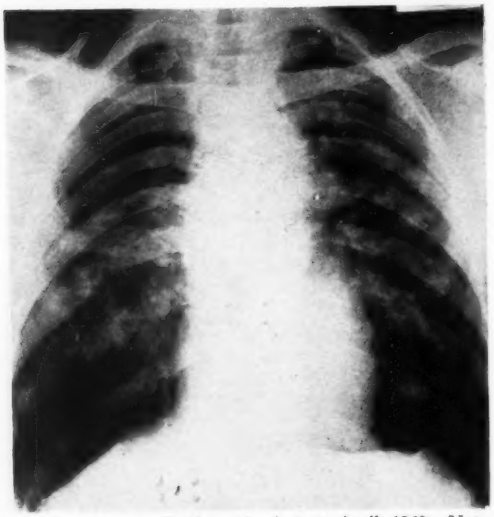

FIG. 12.—Case 5. Radiograph of chest, April, 1960. Note calcification at right apex and at both hila.

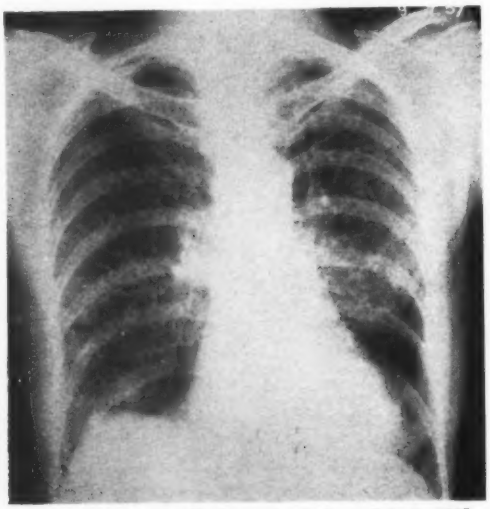

FIG. 13.—Case 6. Radiograph of chest, July 9, 1957.

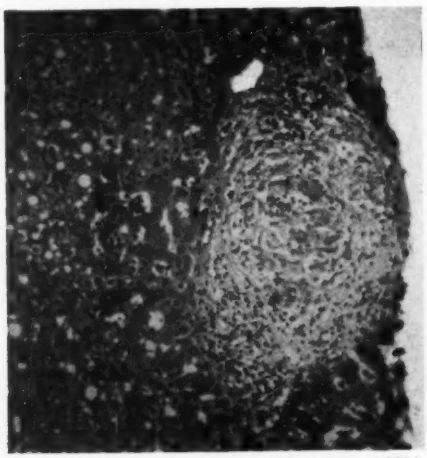

FIG. 14.—Case 6. Liver biopsy. (H. and E. ×200.)

various groups for purposes of description is artificial and seems to me to correspond to no real difference between them, so I believe that no clear line of demarcation can be drawn between sarcoidosis and certain cases which would be accepted without question as indolent tuberculosis with low tuberculin sensitivity. In 1956 I described a group of four cases of tuberculin-negative pulmonary tuberculosis, and drew attention to the difficulty of distinguishing sharply between such cases and some of the cases of sarcoidosis in which tubercle bacilli had been found (Scadding, 1956). A similar conclusion was reached by Zettergren (1954) in relation to the histology of lymph-nodes. He compared 54 lymph-nodes from cases of sarcoidosis with 49 lymph-nodes affected by chronic hyperplastic tuberculosis, distinguished by the microscopic identification of acid-fast bacilli in them; and concluded that the two groups could not be distinguished histologically. Where there is such difficulty in deciding into which of two categories such cases should be placed, we may well consider whether the two categories may not in fact overlap; and I have already shown that logically there is no reason why the categories "tuberculosis" and "sarcoidosis" should be mutually exclusive.

In relation to the hypothesis that sarcoidosis may be an unusual reaction to a tuberculous infection, cases of undoubted pulmonary tuberculosis which show features, such as insensitivity to tuberculin, normally associated with sarcoidosis but not with caseating tuberculosis are highly significant in spite of their rarity. Another even rarer type of case with significant atypical features is that in which tuberculosis, bacteriologically proved, fails to respond to antibacterial drugs though the bacilli are sensitive to the drugs used, and there are none of the features, such as overwhelming infection, usually associated with such failure. I will quote two such cases.

Case 6

A woman aged 61 had been feeling tired for a year, had become breathless on exertion, lost weight for six months, and been feverish for two months, when she was admitted to hospital in May, 1957. She looked moderately ill and was febrile. A chest radiograph showed faint miliary shadowing, though a film taken a month previously had been clear. Full doses of streptomycin, isoniazid, and P.A.S. were given, but the fever persisted and the shadows in the radiograph became denser (Special Plate, Fig. 13). No tubercle bacilli were found on culture of two laryngeal swabs and three gastric-lavage specimens. She was transferred to the Brompton Hospital on July 8. Fever swinging up to 101° F. (38.3° C.) persisted. The Mantoux test showed a moderate reaction to 10 t.u. Continuation of full doses of the three antibacterial drugs produced no change in the fever or the general condition, and the radiographic shadows grew denser. On August 6 a liver biopsy (Special Plate, Fig. 14) showed many non-caseating tubercles. On August 21 prednisolone, 40 mg. daily, was added to the treatment, with immediate fall in temperature and erythrocyte sedimentation rate to normal and clearing of shadows from the chest radiograph. On August 28 a lesion resembling a choroidal tubercle was seen in the right fundus oculi. About this time reports were received that cultures of two sputa taken in July had produced tubercle bacilli sensitive to all three drugs. The prednisolone was very gradually reduced, and finally stopped in March, 1958; she continued taking isoniazid and P.A.S. until January, 1959, and when last seen in May, 1960, was well, with faint residual mottling in the lungs but no important symptoms.

This patient was clearly suffering from subacute miliary tuberculosis and was not critically ill. Nevertheless the disease progressed in spite of prolonged treatment with antibacterial drugs to which her bacilli were sensitive, and responded rapidly to corticosteroid treatment. Though no explanation can as yet be advanced for this peculiar response to treatment, the occurrence of even a single case of this sort disposes effectively of the argument that, because sarcoidosis does not respond to antituberculosis drugs and may show remissions under corticosteroid treatment, the tubercle bacillus can play no part in its causation.

The following case could be used alternatively either to illustrate this theme once more, or as another example of the group in which sarcoidosis followed caseating tuberculosis. I have not at present grouped it as a case of sarcoidosis, because we have not yet detected any manifestations outside the lungs, and the distribution of the disease as first shown radiographically was that usually associated with caseating tuberculosis rather than with sarcoidosis.

Case 7

A woman aged 36 was found in January, 1958, on routine radiography, to have fine mottled opacities at the apices of both lungs, especially the left. She had no symptoms. Her skin reacted to 10 t.u. From one out of seven laryngeal swabs tubercle bacilli were grown, sensitive to streptomycin, ioniazid, and P.A.S. She was treated for two years with isoniazid and P.A.S., and with streptomycin as well for the first month. There was no change in the radiographic shadows during this time. Tomographic appearances of the apices of the lungs in February, 1958, and in February, 1959, after one year of treatment, were identical. The treatment was stopped in January, 1960. In April, 1960, the fine mottling was observed to have spread into the middle zones of the lungs, and the radiographic appearances were more like those usually associated with sarcoidosis.

Cases in which features diagnostic or suggestive of overt tuberculosis and others more usually associated with sarcoidosis are inextricably mixed are far from uncommon. In 1957, with my colleague, Dr. K. M. Citron, I published three cases under the title "Stenosing Non-caseating Tuberculosis (Sarcoidosis) of the Bronchi" (Citron and Scadding, 1957a). These were clinically very similar to each other; all had, in addition to the bronchial changes, sarcoid-type histological changes in one or more sites outside the thorax. In one the skin persistently showed low or absent sensitivity to tuberculin, and no tubercle bacilli were isolated; in the second the skin showed moderate sensitivity to tuberculin, and no tubercle bacilli were found; and in the third the skin was persistently insensitive to tuberculin, but tubercle bacilli were found on two occasions, and the histology of mediastinal lymph-nodes was thought suggestive of very chronic caseating tuberculosis. There is no diagnostic category with a generally agreed name into which can be placed cases in which, individually or as a group, there is evidence that sarcoidosis has developed as a result of infection by *M. tuberculosis*. I suspect that lack of a convenient name for such cases leads to their being left out of consideration, so that a sharp distinction between the clinical concepts of "tuberculosis" and "sarcoidosis" is maintained simply by our verbal habits. I suggest that these cases can properly be termed "mycobacterial sarcoidosis."

Tuberculin Sensitivity in Sarcoidosis

One of the few facts about sarcoidosis which is generally agreed is that skin sensitivity to tuberculin and to other substances producing similar delayed reactions is depressed as compared with that of unselected control groups. This can be explained on one of two

hypotheses. One of these is that sarcoidosis, caused by some unidentified agent, depresses this sort of sensitivity non-specifically just as do Hodgkin's disease and some other diseases affecting the reticulo-endothelial system (Hoyle *et al.*, 1954). On this hypothesis it would be expected that those patients with sarcoidosis, in whom evidence of past or present tuberculosis can be found, would show a generally higher level of tuberculin sensitivity than those in whom no such evidence is available; but, as I have already shown, in my series this is not so, the distributions of sensitivity to various doses of tuberculin in these two groups being the same. A similar observation was made in the course of an investigation of the effect of cortisone on tuberculin reactions in sarcoidosis. Pyke and Scadding (1952) found that in about 50% of patients with sarcoidosis who were insensitive to tuberculin the addition of cortisone to the tuberculin would cause a reaction. Citron and Scadding (1957b) confirmed this observation in 28 further patients, who all failed to react to 100 t.u., but of whom 14 reacted and 14 did not react to tuberculin plus cortisone. Twelve of them had clear evidence of previous tuberculous infection, either in the form of calcified foci in the lungs or hilar lymph-nodes or of the previous finding of tubercle bacilli. If sarcoidosis is due to an unknown agent which incidentally depresses tuberculin-type reactions, it would be expected that, since these 12 patients presumably had at one time reacted to tuberculin, they would be found predominantly in the group who in the sarcoid phase reacted to tuberculin when cortisone was added to it. In fact, rather less than half of them fell into this group, 5 reacting and 7 not reacting to tuberculin plus cortisone; while of the 16 patients in whom no positive evidence of earlier tuberculosis was found, 9 reacted and 7 did not react.*

These observations support the second possible explanation of the low sensitivity of patients with sarcoidosis to agents producing tuberculin-type reactions—namely, that the depression of the capacity to react in this way is one aspect of the peculiarity of the tissue reactivity of these patients which determines that they develop sarcoidosis in response to an agent or agents more commonly associated with changes of another type. The other observations which I have described on the evidences of tuberculous infection found in some patients with sarcoidosis seem to me to lead to the conclusion that the tubercle bacillus is among these agents. I am impressed by the way in which what I have called the sarcoid and the caseating phases are inextricably intermingled; and also by the arbitrariness of the distinction between sarcoidosis and indolent tuberculosis with low tuberculin sensitivity, as shown by certain cases which could with equal propriety be placed in either of these categories.

External Agents and Host Reactivity in Sarcoidosis

It is my opinion that, both in the patients in whom tubercle bacilli were found in the sarcoid phase and in those in whom there was evidence of caseating tuberculosis before or after the sarcoid phase, the entire illness was attributable to the tubercle bacilli. On this supposition, the reason for the development of sarcoidosis rather than caseating tuberculosis rests in a peculiarity of the tissue reactivity of the patient. In those patients in whom a change from caseating to sarcoid phases or vice versa was observed this peculiar tissue reactivity must be supposed to have developed or disappeared during the observed course. This seems much more plausible than the alternative hypothesis that the disease in these cases is due to two agents, the tubercle bacillus and an unidentified agent causing sarcoidosis. This would imply a most curious mutual antagonism between the two agents; for the whole variety of interrelationships between sarcoidosis and tuberculosis could be explained only by postulating, first, that the unknown agent alleged to cause sarcoidosis is able not only to depress tuberculin sensitivity but also actually to suppress the activity of tuberculous infection; and, secondly, that if tuberculous infection escapes from this suppression it in turn can suppress the hypothetical agent of sarcoidosis.

Thus I accept the proposition that at least some cases of sarcoidosis are a manifestation of a tuberculous infection; or, to express the same proposition from another viewpoint, that the tubercle bacillus can cause sarcoidosis in some subjects. This implies that only a minority of individuals whose reactivity to the infection is or has become peculiar in the appropriate way will develop sarcoidosis. It follows, further, that there are no grounds for denying the possibility that other known or as yet unknown agents, besides the tubercle bacillus, may also be capable of causing sarcoidosis in such individuals. There is at least one report of a patient with sarcoidosis who later developed overt histoplasmosis (Israel *et al.*, 1952), rather as some have proceeded to caseating tuberculosis, suggesting the possibility that *Histoplasma capsulatum* might be considered in endemic areas as one among these possible other infections. This view of the aetiology of sarcoidosis suggests an analogy with erythema nodosum, in which a well-defined clinical syndrome, with equally well-defined and constant histology, can be caused by a variety of external agents, but depends for its production upon the appropriate reactivity of the host.

Thus, in sarcoidosis the study of the peculiar reactivity of the host may be as important as the search for external causative agents. Much work has been done on the ways in which the immune mechanisms of patients with sarcoidosis differed from those of normal persons. It is generally agreed that they show a poor response to antigens causing delayed tuberculin-type responses, including trichophytin, mumps virus, and pertussis agglutinogen (Sones and Israel, 1954), and *Candida albicans* antigen (Citron, 1957). They fail to react to, and do not become tuberculin-sensitive after, B.C.G. vaccination (Lemming, 1940)—an observation which has been confirmed in five cases in my series. On the other hand, they may suffer from diseases associated with sensitivity to antigens producing immediate reactions; several of my patients have also had asthma or eczema. They also produce agglutinins normally after typhoid vaccine (Sones and Israel, 1954), and have been reported to produce higher titres of isoagglutinins in response to mismatched blood than normal individuals (Sands *et al.*, 1955). The hyperglobulinaemia first described by Harrell and Fisher (1939) and

*Since this lecture was delivered Fairley and Matthias (1960) have filled a gap in these arguments. Investigating the effects of cortisone upon skin sensitivity to tuberculin in reticuloses, they found that 62 (45%) of 138 patients failed to react to 100 t.u. The addition of cortisone produced small "positive" reactions in only 5 (8%) of these 62 patients, and in a similar proportion (one out of 14) of tuberculin-negative controls. They compared these proportions with the 50% of tuberculin-negative sarcoidosis patients of Pyke and Scadding (1952) and Citron and Scadding (1957) in whom positive reactions were produced by the addition of cortisone, and concluded that "the mechanism of suppression of tuberculin sensitivity in sarcoidosis is different from that in the reticuloses"

subsequently generally confirmed as occurring in a varying proportion of cases of sarcoidosis may be explicable on the basis of hyperactivity of some aspects of the immune mechanisms. In summary, the altered reactivity of patients with sarcoidosis is complicated, the diminution in sensitivity to antigens producing delayed-type reactions being accompanied by normal or even increased immunological reactivity in some other respects.

I have evidence in one patient that the unusual reactivity preceded the development of sarcoidosis. This was a student nurse who developed clinical signs of sarcoidosis one year after B.C.G. vaccination had twice failed to produce skin sensitivity to tuberculin.

As to the factors which cause patients to develop the unusual reactivity we remain in ignorance. Recently Cummings and Hudgins (1958) have suggested that pine pollens may have some relation to the development of sarcoidosis. This is on the basis of a correlation between the geographic distribution of a large series of cases of sarcoidosis in the United States with that of forests (Michael *et al.*, 1950; Gentry *et al.*, 1955; Cummings *et al.*, 1956); of the finding of acid-fast lipid and an amino-acid resembling diaminopimelic acid in pine pollen; and of the production in animals of epithelioid-cell granulomata by pine pollen and by a phosphatide fraction of pine pollen. If a correlation between exposure to pine pollens and increased liability to sarcoidosis is confirmed, I would suggest, speculatively, that it may be explicable on the hypothesis that contact with pine pollens may be a factor in causing the altered reactivity which determines the development of sarcoidosis in response to infection with *M. tuberculosis* and possibly some other agents.

Summary

To summarize the general view I have tried to put forward on the aetiology of sarcoidosis:

1. Free discussion of aetiology demands a descriptive definition based upon morbid histology.

2. Such a definition will include some cases in which there is good evidence that sarcoidosis is a manifestation of tuberculous infection. The evidence for this in my series of 230 cases consists in the finding of tubercle bacilli in the sarcoid phase in 18; in preceding caseating tuberculosis in 11; and in the change from a sarcoid to a caseating phase, with the appearance of tubercle bacilli, in 5.

3. Indirect evidence leads me to the tentative opinion that most of the cases of sarcoidosis I see in England are of the same aetiological group. The evidence for this is their similarity to those in which direct evidence was obtained; the impossibility of detecting any clear distinction between indolent tuberculosis with low tuberculin sensitivity and sarcoidosis; and the similar distribution of reactions to graded doses of tuberculin in those patients with sarcoidosis who have and have not detectable direct evidence of present or past infection with *M. tuberculosis*.

4. The objection that *M. tuberculosis* cannot be aetiologically related to sarcoidosis because sarcoidosis does not respond to antituberculosis drugs and may be suppressed by corticosteroids is met by the observation that some, admittedly very rare, cases of undoubted tuberculosis behave in the same way in relation to these agents.

5. The cause of sarcoidosis must be sought as much in the altered reactivity of the host as in external causative agents.

6. There may well be other agents, known and as yet unknown, besides the tubercle bacillus which can cause sarcoidosis in a susceptible individual. If such a multiplicity of agents exists, the proportion of cases of sarcoidosis associated with each of them may be expected to vary from one part of the world to another. Hence statements about aetiological agents in sarcoidosis can be accepted as valid only for the population from which the cases on which they are based are derived.

I am much indebted to the many colleagues, both at Brompton and Hammersmith Hospitals, and in chest clinics throughout the country, who, knowing my interest in the subject, have referred to me cases of sarcoidosis and have co-operated in following their progress.

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"The Division of Medical Research has no laboratories of its own; its activities are confined almost entirely to the support of extramural research in the universities and their affiliated institutions. . . . The policy of providing increased support to scientific personnel working in the universities has been continued. In 1959, the number of Medical Research Associates was increased by four, thus bringing to 16 the number of highly qualified medical scientists supported in universities on a continuing full-time basis. . . . Forty-five Graduate Medical Research Fellowships were awarded to enable young medical graduates to take research training in the basic medical sciences. A limited number of postdoctoral Medical Research Assistants were also employed under grants-in-aid to senior investigators. . . . Allocation of Divisional funds was as follows: grants-in-aid of research supported on an annual year-to-year basis $627,485 (32%); 1959 instalments of research grants for terms of three years or longer $847,036 (43%); non-recurring equipment grants $222,968 (11%); Medical Research Associateships $134,751 (7%); Graduate Medical Research Fellowships $147,100 (7%)." (*Forty-third Annual Report of the National Research Council of Canada, 1959–60.*)

RUPTURED VENTRICLE

INCIDENCE IN POPULATION OF LONDON, 1957–8

BY

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AND

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Spontaneous rupture of the ventricle has been recognized as a cause of sudden death at least since the time of Harvey, who described a case (Willis, 1847). Many papers have been written in modern times concerning its incidence and pathogenesis. Krumbhaar and Crowell (1925) published a series of 35 cases (with an analysis of over 600 from the literature), and this series was supplemented by Davenport (1928), bringing its number to 92. The whole series had more male than female cases and the majority were elderly. The authors found that rupture occurred most often on the anterior surface of the left ventricle, and they demonstrated that severe coronary artery disease with occlusion was almost invariably the underlying cause.

In subsequent papers there is no agreement on the relative incidence in the two sexes, but in most there is an increase of numbers with age. Beresford and Earl (1930), describing 46 cases from the records of Tooting Bec Hospital, a large mental institution with many senile inmates, found an excess of females; they believed there was a specially high incidence among mental patients. Jetter and White (1944) also reported a high incidence of ruptured heart in a series of sudden deaths in mental patients, but they found more cases in men than in women. Friedman and White (1944) published details of 10 cases from the post-mortem records of the Massachusetts General Hospital: 7 were male and 3 female; the average age was 66 years. However, Oblath *et al.* (1952), in a series of 80 cases, gathered from the records of the Los Angeles County Hospital over a period of 10 years, found a preponderance of female cases, especially in very old age. Wessler *et al.* (1952) reported 11 male and 9 female cases and exhaustively reviewed the literature; they list many other surveys, some from large general hospitals, some from mental institutions, and some from coroners' material; they conclude that the sex incidence is equal in spite of the higher rates of classical myocardial infarction in men. Recently there have been further publications mainly connected with anticoagulant therapy (Maher *et al.*, 1956; Aarseth and Lange, 1958; Capeci and Levy, 1959). There is disagreement about the effects of anticoagulants, but it is generally accepted that the number of cases is increasing, probably owing to such therapy (Kohn, 1959; Sigler, 1960).

Present Study

The wide differences in the literature on the age and sex distribution of spontaneous rupture of the ventricle and in the estimates of its frequency are due to "selection" in the material, to the varying chances of post-mortem examination being made in cases of sudden death, and to bias in the type of hospital studied. The discrepancies must be further aggravated by the use of simple *hospital numbers* as basis for estimates of *population frequency rates*; it is these that are involved in statements that a disease has a different incidence in the two sexes or at different ages.

In the course of a study of the historical trends of coronary disease (Morris, 1951) data on the incidence of ruptured ventricle were collected. Those for London have now been brought up to date, giving an estimate of the actual incidence of the condition based on a defined population. The figures illustrate how the epidemiological method may clarify the natural history of disease and help to "complete the clinical picture" (Morris, 1957).

Information about deaths from spontaneous rupture of the ventricle in 1957 and 1958 has been obtained for the London (London County Council) area with its population of about 3¼ million. First, the post-mortem records of over 95% of the hospitals in the area, including the 13 main teaching hospitals, were examined. Secondly, records were obtained of the cases occurring among all the necropsies carried out by several coroners' pathologists; these amounted to a 65% sample of all necropsies in the coroners' mortuaries. In London close on 100% of cases of unexplained death from apparently natural causes are examined *post mortem*, mostly in the coroners' mortuaries.

Anticoagulant treatment was noted but no attempt made to obtain details: the information is probably complete for the hospital data, and in the coroners' cases it can be assumed that anticoagulants were not in use, as the deaths were unexpected and usually in persons not under medical care.

Results

Tables I and II show the distribution of cases by sex, age, and place of necropsy. (A few necropsies were made for the coroner in various hospitals; these have been included with the rest of the hospital cases.) Table III scales up the figures to give estimates of the total cases recognized in London during the two years. It will be seen from the tables that this is a cause of death in old rather than middle age. The sex ratio varies with age: under 70 years (Table III) men predominate with a ratio that may be estimated at 114 males:68 females (1:0.6), but over 70 years the position is reversed and the estimated ratio is 160 males:272 females (1:1.7).

TABLE I.—*Number of Cases of Spontaneous Rupture of Cardiac Ventricle Found in London Hospitals, 1957–8*

Age	13 Main Teaching Hospitals*		Other Hospitals (>95% Sample)	
	Male	Female	Male	Female
45–54	—	—	1	—
55–64	10	3	5	2
65–69	5	1	6	2
70–74	3	2	2	6
75–79	1	8	3	7
80–84	—	3	4	3
85+	—	—	1	2

"London" throughout refers to the London County Council area and population.
* Twelve undergraduate hospitals and Hammersmith Hospital.

TABLE II.—*Number of Cases of Ruptured Ventricle Found in London Coroners' Mortuaries, 1957–8*

Age	Male	Female
45–54	7	1
55–64	21	20
65–69	28	18
70–74	30	45
75–79	29	43
80–84	18	36
85+	17	32

These cases were found in a 65% sample.

TABLE III.—*Number of Cases of Ruptured Ventricle Found in London, 1957–8: Estimated Total*

Age	Male			Female			Total		
	Hospitals	Coroners' Mortuaries	Total	Hospitals	Coroners' Mortuaries	Total	Hospitals	Coroners' Mortuaries	Grand
Under 70	28	86	114	8	60	68	36	146	182
70+	15	145	160	32	240	272	47	385	432
Total	43	231	274	40	300	340	83	531	614

The hospital and the coroners' figures have been scaled up to 100%. It was not considered worth attempting any adjustment for London cases examined outside the area, and non-London cases examined inside it.

Table III, with its approximate totals, also shows that only a small minority of cases were seen in hospital—rather less than 15%—and, with Table I, that the hospital experience, in particular the teaching hospital experience, differs from the total in both sex and age distribution. There is no overall preponderance of female cases in hospital, as is seen in the coroners' and total data. This is mainly due to the excess in number of males under 70 among teaching-hospital cases: and this excess also produces a biased age distribution particularly in these hospitals, with too many in middle age. Of the 13 cases that were known to have had anticoagulant therapy (11 men, 2 women), 7 were men in the middle-aged hospital group.

Finally, estimates of annual sex and age incidence *rates* that are probably accurate enough for epidemiological purposes are given in Table IV. The present

TABLE IV.—*Ruptured Ventricle in London. Estimated Average Annual Incidence per* 1,000 *Population*, 1957–8

Age	Male	Female
45–54	0·03	(0·004)
55–64	0·2	0·1
65–69	0·5	0·2
70–74	0·6	0·6
75–79	0·9	0·8
80–84	1·2	1·1
85+	2·4	1·8

Cases from Table III. Population estimates were kindly provided by Mr. C. W. Shaddick.

data, scaled up to 100%, have been related to 1957–8 population estimates for the L.C.C. area. Incidence in men is higher than in women during middle age (though there are so few deaths in women from this cause at 45–54 that the rate is "unreliable"), but there is little difference after 70 years. This finding is factual support from pathological and epidemiological evidence for the clinical impression that the excess of coronary heart disease in males over females is reduced after the menopause and tends to disappear in old age. There are so many more old women than old men in the population (Registrar-General, 1960a) that a greater number of female *cases* in old age merely produces near equal *rates*.

Clinical Histories

Ruptured ventricle is thus a relatively frequent cause of death in the aged, and a study of the clinical histories gives some indication why these cases are commoner in coroners' post-mortem material than in hospital. In most cases death seems to have occurred with few prodromal symptoms, and these were not very specific. Here are typical stories:

1. Woman 78 years. Complained of "indigestion pain" two weeks before death but otherwise seemed well. Found dead on the floor.

2. Man 68 years. Pain in left shoulder five days before death. This was thought to be rheumatic. On day he died he felt sick in the morning, but this passed off. Died about noon.

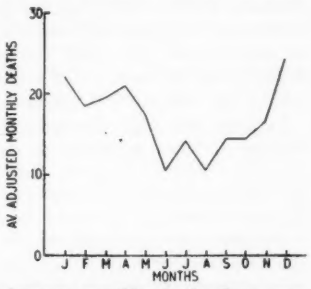
3. Woman 74 years. Some "indigestion pains" for one week; otherwise well. Dropped dead while out shopping.

4. Woman 75 years. Neighbours noticed milk bottles not taken in for several days. Found dead in bed.

5. Woman 84 years. Complained of tiredness for a few days, but up and about. Died suddenly.

With such clinical histories, it is possible that the number of cases recognized underestimates the real total.

The *seasonal trend* shown in the Chart is characteristic of mortality as age advances. It was noted in both the years studied that there were twice as many ruptured hearts in December and January as in the summer months.



Average monthly deaths from ruptured ventricle. London, 1957–8. Frequencies have been adjusted to number of days in month.

Pathological Findings.—At necropsy, pathological evidence of hypertension was very commonly noted and a history of diabetes frequently mentioned, but because of the nature of these deaths there are no reliable data on blood-pressure and associated conditions during life (likewise, retrospective social analysis proved impracticable). In more than half the cases the rupture had taken place through the anterior wall of the left ventricle and in about a quarter through the posterior wall; in the rest the site of rupture was lateral, antero-lateral, postero-lateral, apical, or undefined. In seven cases the rupture was in the right ventricle. Very severe coronary atheroma, and coronary occlusion, were usually reported.

In the course of the whole study 10 cases of *septal* rupture were collected. They have been excluded from the tables as they usually present with a different history (Sager, 1934; Armanious, 1960), death being delayed often for two or three weeks. Of the 10, 5 were in men and 5 in women.

Discussion

This paper is concerned with the frequency and distribution of this manifestation of ischaemic heart disease. It illustrates in gross degree the selection which may be present in hospital material and, in particular, it indicates how unrepresentative the post-mortem material of teaching hospitals, the source of most statements on morbid anatomy, may be. The main teaching hospitals each had, on average, between one and two cases a year of this condition during the two years studied; six of them, in fact, had only one case during the two years or none at all. The total hospital data show "selection" with regard to age, sex, and anticoagulant therapy. Such selection, together with the real variation of the sex ratio with age—and sheer inadequacy of numbers—presumably explains the conflicting statements in previous series. The high incidence in mental patients may also have been due to selection, more necropsies being done on mental patients, particularly in America; moreover, such series

would inevitably deal with an undue number of the very aged (Registrar-General, 1960b). No excess incidence in mental patients was found in the present study, and although special data from the large mental hospitals in the Surrey area were obtained (not reported) there still appeared to be no excess. However, no attempt has been made to prove this.

Four points about ruptured ventricle have been brought out by the use of a *population study* rather than the *collection of clinical cases*: (1) Spontaneous rupture of the ventricle is a common post-mortem finding. The estimates given here are for cases recognized at necropsy and therefore minimal. (2) In London it is a problem of the coroners' mortuaries rather than the hospitals. Once again the disadvantage of studying ischaemic heart disease in hospitals alone is illustrated (Morris, 1951). (3) The incidence rises with age in both sexes; it is rare in middle age but a frequent cause of death in old age. (4) The largest number of cases occur in old women, but the true incidence during old age in the two sexes is similar.

Interest nowadays is focused on the post-mortem finding of ruptured heart in relation to anticoagulant therapy. The evidence is that, whether increasing or not, these cases form a tiny fraction of the total. The figures presented—13 cases in the two years—provide a baseline, and it should be possible in a few years to estimate whether a real increase is occurring in London in relation to the increasing use of anticoagulants, which is likely.

Summary

The incidence of ruptured ventricle due to ischaemic heart disease among the 3¼ million population of London has been studied. It may be estimated that about 600 cases were recognized in London during 1957 and 1958. If the London figures are typical of the country as a whole there may be about 5,000 cases a year in Great Britain or about 100 cases per million of population. The condition is thus by no means rare; it probably causes about 1% of deaths in old people. Because of the nature of the clinical history in old people these figures are likely to be an underestimate.

The incidence of ruptured ventricle rises with age in both sexes. In *middle* age there are more cases in men than in women, and the incidence rate, per 1,000 of the population, is more than double that in women. In *old age* there are more cases in women than in men, but the incidence is probably about equal in the two sexes.

The great majority of the cases in London are seen in the coroners' mortuaries. Hospitals deal with less than 15% of the total, and the sex and age distribution of their cases is atypical: in particular there is a disproportionate number in middle-aged men. Cases associated with anticoagulant therapy form a small minority, about 2% of the total; they are grossly over-represented in the hospital data.

In more than half the cases rupture occurred through the anterior wall of the left ventricle; in about a quarter through its posterior wall.

The analysis illustrates how the epidemiological method can help to correct and complete the clinical picture of a disease and its natural history.

We are greatly obliged to Dr. F. E. Camps, Department of Forensic Medicine, London Hospital Medical College; to the professors of pathology in the teaching hospitals, the consultant pathologists, and the coroners' pathologists of London, and to their medical and lay colleagues, for free access to their records and much other help; to Mr. C. W. Shaddick, statistician, Public Health Department, London County Council, for population estimates and much other help; and to our colleagues in the Social Medicine Research Unit.

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RUPTURE OF THE HEART

BY

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Rupture of the heart is a dramatic complication of myocardial infarction, and the knowledge that it may occur has undoubtedly influenced the management of other cases of myocardial infarction with regard to the degree and duration of rest, the length of stay in hospital, and the activities permitted during convalescence.

To try to define the factors which may cause an infarcted heart to rupture we have studied 215 cases of ventricular rupture occurring in two teaching hospital groups and in a series of sudden deaths investigated by the coroner of a large industrial city.

Methods

The records of two groups of patients were examined.

Hospital Series.—Patients who were found at necropsy to have died from rupture of the heart in the years 1939–59 at the Radcliffe Infirmary, Oxford, and the Queen Elizabeth and General Hospitals, Birmingham.

Coroner's Necropsy Series.—From the records of all the post-mortem examinations carried out on the instructions of H.M. Coroner for the City of Birmingham in the years 1951–60, information was obtained on two groups of patients. (*a*) All patients

who, at necropsy, were found to have died from spontaneous rupture of the heart. (*b*) A 1-in-9 random sample of those cases in which recent thrombotic occlusion of a coronary artery, or established myocardial infarction, had been specified in the necropsy record. Cases described as coronary atheroma and coronary insufficiency were not included.

Results in Hospital Series

Incidence.—3,790 patients with myocardial infarction were admitted to the three hospitals in the years 1939–59, and during this period there were 46 ruptures of the heart, an incidence of 1.2%.

Sex.—15 (32.6%) of the patients with cardiac rupture were male, and 31 (67.4%) female. The sex ratio differs significantly ($p<0.001$) from that of the patients with myocardial infarction admitted during the 20-year period, of whom 2,724 (71.9%) were male and 1,066 (28.1%) female.

Age.—The mean age of the women was 69.5 ± 1.4 years; that of the men was 64.9 ± 2.2 years. This difference is not statistically significant ($p=0.09$), and the numbers are too small to permit the age distribution to be compared with the age distribution of the cases of cardiac infarction admitted during the 20-year period.

Blood-pressure After Infarction.—Edmondson and Hoxie (1942) suggested that patients whose blood-pressure did not fall after infarction were especially prone to cardiac rupture. The blood-pressure before infarction is seldom known, and it is therefore difficult to decide whether a drop in pressure has occurred. However, if Edmondson and Hoxie are correct, the readings on admission should resemble those of a random sample of the general population. Hamilton *et al.* (1954) studied such a sample in detail and suggested that it could be used as a basis for comparison by making a simple correction for the effects of age and sex. The difference, in millimetres of mercury, between a given blood-pressure reading and the expected value for a person of that sex and age, as determined by Hamilton *et al.*, is known as the age and sex adjusted score. If the pressure levels of the test group are similar to those of the general population, the differences and scores should be grouped around zero.

The blood-pressure on admission had been recorded in 38 patients, and we have converted these readings into adjusted scores (Fig. 1). The systolic levels are clearly shifted to the negative side of the mean (29 patients had minus scores of 10 mm. Hg or more, compared with 9 patients with scores of zero or above). The diastolic scores show a similar but less marked deviation (21 patients had minus scores of 10 mm. or more, compared with 17 patients with scores of zero and above). The blood-pressure levels after infarction are therefore lower than one would expect to find in a random sample of the general population, the systolic shift being more pronounced than the diastolic. This does not support the contention that the patients whose hearts are ruptured are the ones who maintain a normal or raised blood-pressure level after infarction.

Electrocardiogram.—This was recorded in 29 patients, and in 28 of them pathological Q waves were present, indicating full-thickness infarction. The pattern in the remaining patient was obscured by left bundle-branch block.

Laboratory Investigations.—25 patients had had blood counts, and in 19 there was a neutrophil leucocytosis of 10,000/c.mm. or more; six patients had a normal leucocyte count. In 15 patients the erythrocyte sedimentation rate had been estimated: seven had rates of over 20 mm./hour (Westergren); and eight had rates of 20 mm./hour or less.

Management of Patients.—(1) *Drugs:* 17 of the 46 patients had been given anticoagulants and 12 had been given digitalis, but in the majority death occurred before therapeutic levels had been reached. (2) *Activity at the time of rupture:* 42 patients were at rest in bed (in 21 of these the rupture occurred during sleep), and four were sitting reading.

Time After Infarction.—In 36 patients the time of the initial infarct could be estimated from the clinical history, and Fig. 2 shows the period that had elapsed between the infarction and death from cardiac rupture. 18 of the ruptures occurred in the first 24 hours, and the longest interval between infarction and rupture was nine days.

Site of Rupture.—This was anterior in 23, posterior in 11, lateral in 3, and septal in 9.

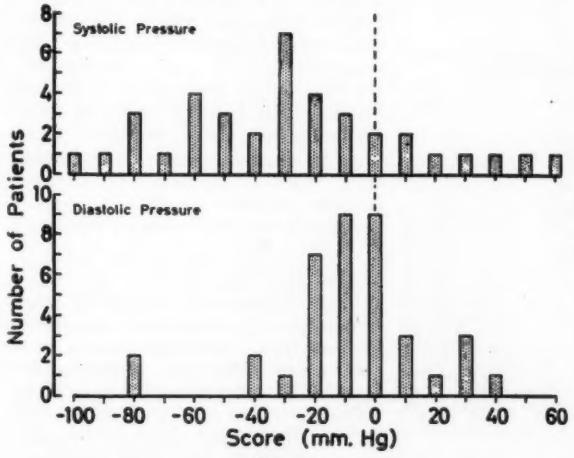

FIG. 1

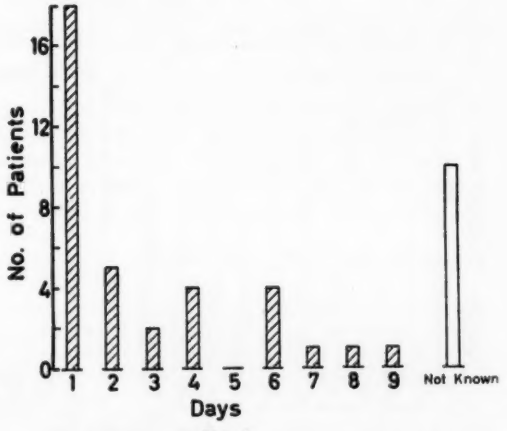

FIG. 2

FIG. 1.—Hospital series. Systolic and diastolic blood-pressure levels recorded on admission in 38 patients who died of cardiac rupture, expressed as age and sex adjusted scores. FIG. 2.—Hospital series. Interval between estimated time of myocardial infarction and death from cardiac rupture.

Results in Coroner's Necropsy Series

Sex Ratio.—The 1-in-9 sample of myocardial infarcts contained 114 men and 40 women; during the same period there were 81 cardiac ruptures in males, and 88 in females. This reversal of the male : female ratio is highly significant ($p<0.001$).

Age distribution for men and women with myocardial infarction and cardiac rupture is shown in Fig. 3. The Table shows the mean ages of the four groups. There

Coroner's Necropsy Series. Mean Age and Standard Error of Mean of Patients with Myocardial Infarction and Rupture of the Heart

	Myocardial Infarction	Cardiac Rupture	Significance of Difference
Male	60·2±1·3	69·7±1·6	p<0·001
Female	69·6±1·8	73·4±1·4	p=0·1
Significance of difference	p<0·001	p=0·1	

is a highly significant age difference between males and females with cardiac infarction, and between males with infarcts and males and females with rupture of the heart. There is no significant difference between females with infarcts, males with cardiac rupture, and females with cardiac rupture.

A more accurate assessment of the incidence of the two conditions at different ages is given by correcting for the number of persons in each age group living in the area (City of Birmingham Abstract of Statistics, 1958–1959). This corrected value is purely arbitrary, but it indicates the relative liability to infarction and rupture. Fig. 4 shows these values and confirms the trend of Fig. 3—the risk of infarction is maximal in males in the 60–75 age-group, and then declines, whereas for females the risk increases sharply over the age of 75. The number of ruptures per 10,000 living persons increases with age in both sexes up to the age of 80, and then shows a slight decline.

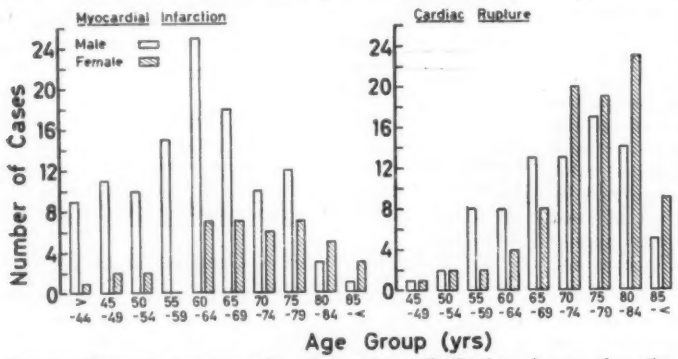

FIG. 3.—Coroner's necropsy series. Age and sex distribution of cases of cardiac rupture and of a random sample of cases of myocardial infarction.

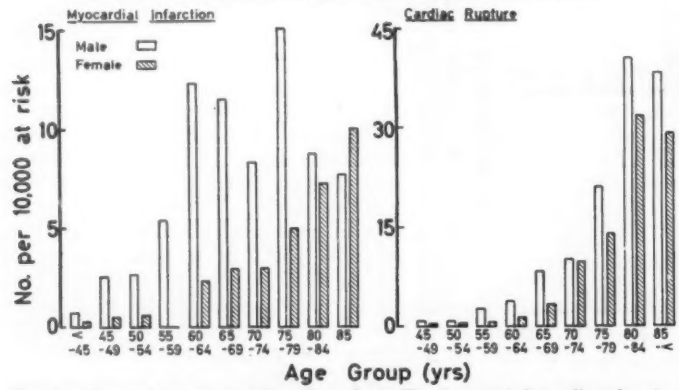

FIG. 4.—Coroner's necropsy series. Data from Fig. 3 corrected to allow for the population at risk in each age-group and expressed as the calculated number of cases per 10,000 living persons.

We have also determined, for each age-group, the ratio between the number of cases of rupture of the heart and the total number of infarcts, including those which ruptured—that is, ruptures ÷ ruptures + myocardial infarcts. The ratio rises steadily with increasing age (Fig. 5), suggesting that in this series of coroner's necropsies the risk of rupture increases with age. The ratio is slightly higher for women, but the difference is not significant. The ratio in women under 60 years of age was not determined, because of the very small number of cases.

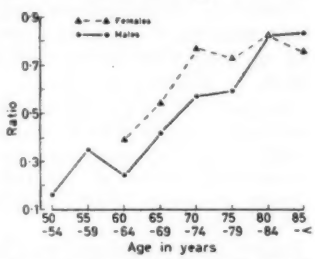

FIG. 5.—Coroner's necropsy series. Ratio between the number of cases of cardiac rupture and cases of myocardial infarction, including those which ruptured, for each age group.

Discussion

Several authors have noted that the sex ratio in rupture of the heart differs from that in myocardial infarction (Beresford and Earl, 1930; Edmondson and Hoxie, 1942; Zinn and Cosby, 1950; Oblath *et al.*, 1952; Wessler *et al.*, 1952). Other authors, reporting smaller numbers of cases, have found a similar trend; and, in all, of the 412 cases of cardiac rupture reported in the literature in which the sex of the patient was stated, 168 were male and 244 female. No satisfactory explanation of this sex difference has been put forward.

Benson *et al.* (1933) thought that it was due to the selective factor of hospital admission, for most of the published series relate to hospital in-patients. They suggested that the men with rupture of the heart might be included in coroners' rather than hospital necropsy series. Undoubtedly many selection factors must be operating; therefore we studied both types of necropsy in order to provide a more complete picture, and perhaps cancel out some of the factors.

There seems little doubt, from our results, that the different sex ratio in cardiac rupture and myocardial infarction is closely linked with the different ages at which infarction occurs in the two sexes. Men are more liable to myocardial infarction in middle age, when the risk of rupture is low. Women, on the other hand, develop myocardial infarcts later in life, when the risk of rupture is high. In addition, the population contains more women than men in

the older age-groups (in the City of Birmingham survey there were 44,000 women, as opposed to 24,800 men, over the age of 70 years). Both of these factors would operate to produce more ruptures of the heart in women than in men.

Although we cannot explain the increased risk of rupture in older patients, we can get some information from the hospital series about the circumstances in which rupture occurs. The maximal risk is in old patients with electrocardiographic evidence of transmural infarction, the first 24 hours after the infarction being particularly critical. There is no evidence to support the view that the patients who rupture are the ones whose blood-pressure remains high after the infarction. The rupture did not relate to physical activity, for most of our patients were in bed, and nearly half were asleep, at the time of rupture.

Summary

215 cases of rupture of the heart after myocardial infarction are reported. The sex ratio (96 male; 119 female) differs significantly from that for myocardial infarction.

This is due to the increasing risk of rupture in old patients and the tendency for women to develop infarcts later in life than men.

The risk of rupture is maximal in the first 24 hours after infarction, and there does not appear to be any correlation with physical activity, digitalis or anticoagulant treatment, or high blood-pressure levels after infarction.

We are grateful to the Records Departments of the United Oxford and the United Birmingham Hospitals for their help with the case-notes, and we are particularly indebted to Mr. G. Billington, H.M. Coroner for the City of Birmingham, for allowing us to make use of his records.

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The publication *Russian–English Scientific and Technical Dictionaries* has been prepared for the National Science Foundation, U.S.A., by Professor A. F. Hubbell. The main chapters are: Types of Interlingual Dictionaries; the Plan of Existing Russian–English Dictionaries and Recommendations for the Improvement of Future Works; the Organization of Lexicographical Projects; Survey of Needs in Particular Fields (Mathematics, Physics, Chemistry, Earth Science, Meteorology, Cartography and Related Fields, Aviation and Aeronautical Sciences, Space Sciences, Military and Naval Sciences and Technologies, Medicine and Medical Sciences, Life Sciences, Miscellaneous Technologies and Engineering Specialties). Copies of this 20-page report may be obtained at 40 cents each (U.S. stamps or Unesco coupons) from Professor A. F. Hubbell, Gallatin House, New York University, New York 3, N.Y., U.S.A.

ALPHA-CHYMOTRYPSIN IN CATARACT SURGERY*

BY

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In a preliminary communication to the Royal Academy of Medicine of Barcelona in April, 1958, Joaquin Barraquer first described the use in ophthalmic surgery of alpha-chymotrypsin, a proteolytic enzyme, to weaken the fibres of the suspensory ligament of the lens and consequently facilitate its removal.

This is undoubtedly a most significant advance in the surgery of cataract, and during the following year publications from every major country testified to the veracity of his findings. There is no doubt that in the living human eye alpha-chymotrypsin, injected into the region of the zonule of the lens, destroys or weakens this structure so that little mechanical force is required to remove the lens.

Possible Bad Effects

The possibility that the use of the enzyme might have bad effects, however, caused equal discussion, which has not led to the same universal agreement.

Firstly, animal and *in vitro* experiments seem to suggest that alpha-chymotrypsin has an effect on other tissues of the eye than the zonule. Salmony (1959) studied the biochemical action of the enzyme on the aqueous, the lens homogenates, and the vitreous of the ox, and on the lens and aqueous of the rabbit, and demonstrated that a fairly rapid breakdown of proteins in all these tissues occurs when incubated with alpha-chymotrypsin. This seems to prove that the effect of the enzyme is not restricted specifically to the zonule but is capable of attacking other structures, such as the vitreous. Appelmans, Michiels, de Backer, and Alaerts (1959) injected alpha-chymotrypsin solution into rabbit corneae and instilled drops containing the enzyme on to corneae denuded of epithelium, and showed that there was a harmful effect on the parenchyma of the cornea. Bégué and Waksmann (1959), using rabbits' eyes, sought to prove that the enzyme affects only the cement substance between zonule and lens capsule. Bedrossian (1959), in his experiments, seemed to prove that there is no ill effect on wound-healing.

Secondly, discussion regarding the clinical findings relating to possible side-effects of the use of alpha-chymotrypsin in the living eye has been even more confused.

The following are the main effects that have been suggested.

1. *Delayed Healing of Wound.*—Barraquer (1959) himself, in his survey of 297 cases, described an increased incidence of delayed re-formation of the anterior chamber. Weekers, Lavergne, and Stassart-Hourlay (1959) also described this complication, but otherwise it does not seem to have troubled many surgeons.

*The work was carried out in connexion with the South-west Metropolitan Regional Hospital Board's Research Competition, 1959, for which it received the principal award.

2. *The Cornea.*—At clinical meetings in the United Kingdom during 1959 much discussion centred around the possibility of an increase of striate keratitis. However, there was no general agreement about the incidence of this complication in cataract extraction with or without the enzyme. Ainslie (1959) pointed out that the use of the mechanical erisophake might be the cause of increased striate keratitis. Deposition of iridian pigment on the back of the cornea was described by Pierse (1959a) and others. Hill (1959) described marked vascularization of the cornea after extraction with alpha-chymotrypsin, but this report relates to a single case only.

3. *The Vitreous.*—Although the most dangerous possibility would seem to be damage to the vitreous there has been little published study of this tissue after extraction using the enzyme. Norbis and Malbran (1958) and Walser (1959) mentioned damage to the anterior hyaloid membrane, but these findings were not conclusive.

The continued plea of many responsible observers in this country has been for caution in the use of this method of cataract extraction until clinical observations over a reasonably long period are available. This study was undertaken to help fulfil this need.

Scope of Present Study

During June to December, 1958, 65 cataracts were operated upon by us, working jointly as surgeon and assistant and using alpha-chymotrypsin in each case. Cases were not selected. We have undertaken an assessment of the complications, operative and post-operative, and the results of these cases; and a careful slit-lamp study of the cases during 1959.

The technique used in the series was as described by Pierse (1959b).

Operative Complications

The number of cases operated on was 65; vitreous loss occurred in 1, and rupture of the capsule during extraction in 4.

In the case of vitreous loss the vitreous was fluid and the loss occurred during the Graefe knife section. The patient had a history of severe injury to the eye during the 1914–18 war. In view of the high percentage of complicated cases in the series, this seemed at the time, and still does in retrospect, a very satisfactory and worry-free series of cases.

Immediate Post-operative Complications

Among the 65 cases, prolapse of iris occurred in 1, mild striate keratitis in 4, hyphaema in 7, iritis in 2, and severe keratitis in 1. Healing was delayed in one case.

Striate Keratitis.—This was regarded as an abnormal complication only if it was present for several days after operation. Occasional very slight haziness of the cornea at the time of first dressing, too indefinite to localize in any layer of the cornea, was not considered. The four cases in which definite striate keratitis occurred would seem to be a normal or low percentage of this complication. They all resolved without any effect upon the vision. Corneal oedema appearing at a later stage is considered in the next stage of the study.

Hyphaema.—There were seven cases of hyphaema, excluding cases in which there were small traces at the time of the first dressing. In three cases hyphaema was caused by external trauma several days after operation. In two others it was associated with diabetes.

Iritis.—There were two cases with an iritis lasting about three to four weeks post-operatively.

Delayed Healing.—This case was possibly due to post-operative trauma. From the clinical appearances it seemed very unlikely that the complication bore any relation to the use of alpha-chymotrypsin.

Severe Keratitis.—This case is considered later in the study.

Visual Results

It is of interest that 24 patients—that is, 37%—suffered either from other pathological conditions in the operated eye or from diabetes mellitus.

The visual acuity in 63 patients after a post-operative period of one year was: 6/6 in 36, 6/9 in 8, 6/12 in 4, 6/18 in 5, 6/24 in 2, 6/6/ in 4, and less than 6/60 in 4. Two were not tested (died before minimum period).

Of the 15 patients with a final visual acuity of 6/18 or worse, in nine it was directly attributable to retinal disease present prior to the extraction, in two corneal conditions existing previously, in two to post-operative trauma by the patient, in one to severe bullous keratitis, and in another to amblyopia ex anopsia.

Slit-lamp Examination

In order to determine if there were any complications in this series of extractions that could be attributed to the use of alpha-chymotrypsin, the cases were examined several times with the Zeiss corneal microscope during 1959. At the same time we examined a number of cases of uncomplicated intracapsular extraction, all of which had a corrected vision of 6/6 and which had been operated upon during the previous two years.

Corneal Oedema and Resultant Opacities

Apart from transient striate keratitis, which has already been considered, there were cases of isolated patches of corneal oedema. This finding is, of course, a common one in cataract surgery with known causes, into which most of our cases fell. The main causes of persistent corneal oedema after cataract extraction, apart from the possibility of alpha-chymotrypsin damaging the endothelium, may be summarized as:

1. *Damage to the Endothelium and Descemet's Membrane.*—Unless care is taken it is easy to damage the under-surface of the cornea with instruments, and especially with the erisophake on account of its relative size. Kirby (1955) and McDonald (1957) have stressed this danger. Descemet's membrane may be torn, allowing aqueous humour to penetrate into the corneal stroma.

2. *Vitreo-corneal or Irido-corneal Contact.* — Small anterior adhesions of the peripheral part of the iris to the cornea in the vicinity of the section are sometimes seen with the slit-lamp after cataract extraction. A proportion of the synechiae develop corneal oedema in the overlying area. If an intact anterior hyaloid membrane herniates through the pupil sufficiently to touch the posterior surface of the cornea, corneal oedema may result. Chandler (1954) has stated that if the intact hyaloid membrane adheres to the posterior corneal surface, corneal oedema almost invariably results, and this may be permanent. Sometimes one sees with the slit-lamp strands of vitreous projecting forwards into the anterior chamber and perhaps touching the posterior surface of the cornea, but this does not seem to cause any corneal disturbance.

3. *Pre-existing Endothelial Dystrophy.*—The worst cases of persistent corneal oedema occur in cases of endothelial dystrophy. This has been stressed by many authors (Chandler, 1954; McLean, 1954).

The safety associated with the low intraocular pressure of modern anaesthesia encourages the surgeon to lift the cornea and perform intraocular manœuvres

under direct vision. In the early stages of using the mechanical erisophake we were in the habit of opening the section widely to introduce the instrument; we think that this was the main reason why we had several cases of striate keratitis and corneal oedema in the present series. Since recognizing this danger we have been careful to lift the cornea only enough to allow the introduction of the erisophake; in the later part of the present series, and during the succeeding year, this was the technique we adopted.

Another factor in the production of striate keratitis may have been the incidental damage to the endothelium when the cannula was introduced into the lower part of the eye in order to inject alpha-chymotrypsin behind the lower part of the iris. We now inject alpha-chymotrypsin only through the iridotomy above.

During the present series we thought it possible that alpha-chymotrypsin might alter the permeability of the corneal endothelium in some way and cause an increased incidence of striate keratitis and corneal oedema. Since changing our technique in the ways described above, however, the incidence of striate keratitis has definitely been lowered, and we have had no serious case of corneal oedema.

During the past year we have had no reason to think that alpha-chymotrypsin was a factor in the production of striate keratitis or corneal oedema. Seven out of 65 cases had persistent corneal oedema and one had vision affected by corneal oedema. In two cases an anterior synechia of the upper part of the iris seems to have been responsible for the oedema. Three cases were probably due to tears in Descemet's membrane. In one case there was oedema for one month which cleared up completely: vision is 6/6. No tears in Descemet's membrane were seen. There was one case of so-called bullous keratitis—persistent marked corneal oedema. The exact cause of this has not been elicited.

Pigment Dispersal

1. *Posterior Corneal Surface.*—Though we regarded the presence of pigment on the posterior corneal surface as a complication of the operation it had no effect on the visual acuity. The findings, in 56 cases, were as follows.

None or very slight pigment	28 (50%) cases
Moderate pigment stippling	20 (36%) ,,
Marked pigment stippling	8 (14%) ,,

2. *Pigment Granules on the Iris* (54 cases).—Several of the cases showed a moderate to marked scattering of pigment over the front of the iris.

No pigment	35 (65%) cases
Moderate amount of pigment ..	14 (26%) ,,
Marked amount of pigment	5 (9%) ,,

3. *Atrophy of the Iris* (53 Cases).—As before, we divided our cases into three arbitrary groups, and the results were as follows:

No iris atrophy	22 (42%) cases
Moderate iris atrophy	24 (45%) ,,
Marked iris atrophy	7 (13%) ,,

4. *Pigment Granules in the Anterior Vitreous* (52 Cases).— 62% of our cases had a moderate or marked amount of pigment in the anterior part of the vitreous. Sometimes the pigment was seen scattered over the front of the anterior hyaloid membrane, but, in addition, pigment granules were sometimes dispersed in the anterior layers of the vitreous.

No pigment in vitreous	20 (38%) cases
Moderate amount of pigment ..	26 (50%) ,,
Marked amount of pigment	6 (12%) ,,

General Consideration of the Pigment Dispersal

We thus found that in this series pigment granules were scattered over the posterior surface of the cornea in 50%, on the front of the iris in 35%, and in the anterior layers of the vitreous in 62% of the cases. 58% of our cases showed areas of iris atrophy, so presumably the pigment had come from these areas. Kara (1959) also described excess pigment deposit on the corneal endothelium and in the vitreous after cataract extraction with alpha-chymotrypsin. In patients who had been operated on without using alpha-chymotrypsin we found that a similar appearance was sometimes seen, but it was not so frequent.

It is possible that our technique of introducing the cannula behind this iris in order to inject the alpha-chymotrypsin into the posterior chamber was the reason for the pigment dispersal, as the cannula must necessarily rub against the back of the iris during this manœuvre.

There was no increase in the pigment dispersal during the year of the review.

No definite conclusions can be drawn from this series of cases. All we would say is that from our experience it seems possible that alpha-chymotrypsin is a factor in the production of pigment dispersal throughout the anterior part of the eye but that no ill effects to the eye result from it.

Size and Mobility of the Pupil in 46 Cases

Pupil Size	No. of Cases	Mobility of Pupil	No. of Cases
2 mm.	8 (17%)	Immobile	4 (9%)
3 ,, ...	24 (52%)	Slightly mobile ..	28 (61%)
4 ,, ...	10 (22%)	Mobile	14 (30%)
5 ,, ...	4 (9%)		

It seems likely that in many cases there are small adhesions between the iris and the anterior hyaloid membrane which are not visible with the slit-lamp; they prevent full mobility of the pupil. Another interesting finding is that if there is a herniation of the anterior hyaloid membrane through the pupil, this becomes more flattened when the pupil is dilated with a mydriatic. This effect is probably also due to these adhesions between iris and vitreous.

The Vitreous Face

Surrounding the vitreous is the so-called hyaloid membrane, the exact nature of which is unknown. Duke-Elder (1940) considers that it is merely a surface condensation of the fibrillar elements of the gel. Cowan and Fry (1932) produced evidence to show that in its anterior portion, at any rate, the hyaloid membrane is a non-nuclear, structureless, uniformly staining membrane.

In our case we examined the anterior hyaloid membrane with two questions in mind: (i) whether the vitreous face was flat, or protruding into the anterior chamber; and (ii) whether the anterior hyaloid membrane was intact or had holes or rents in its surface.

After cataract extraction the anterior surface of the intact vitreous face behaves as if it was limited in front by a definite membrane. Even with the highest magnification of the Zeiss corneal microscope, however, no actual membrane can be seen. The position and contour of the anterior hyaloid membrane is judged by means of pigment granules on its surface and slight opacities of the vitreous itself. If these are absent it is difficult and sometimes impossible to judge the position of the anterior hyaloid membrane accurately.

Protrusion of the Vitreous Face

It is well recognized that herniation of the anterior hyaloid membrane is common after cataract extraction (Berliner, 1949; Hilding, 1954). Leahey (1951) made a survey of 100 unselected intracapsular extractions and found that 39% showed a herniation: in 13% the anterior hyaloid membrane was touching the cornea, though in most of these the contact was merely a peripheral one at the top of the complete-iridectomy area. Irvine (1953) found that only 54% of post-cataract cases had a flat and intact vitreous face.

These figures agree fairly closely with our own in this series. Our findings in 57 cases were:

Flat or slightly convex	31 (54%) cases
Moderate protrusion	13 (23%) „
Marked protrusion	13 (23%) „

In no case in the series was an intact vitreous face touching the back of the cornea.

The surface of a protruding vitreous face is often lightly speckled with pigment granules. Sometimes the whole protrusion is quite mobile. Undoubtedly, trauma during the operation is more likely to produce such protrusions, but trauma is not necessary for their occurrence, and even after the most satisfactory and easy extraction it is not uncommon to find a herniation of vitreous face. Such vitreous protrusions become flatter in time. This occurs gradually over several months. We noted this flattening of a vitreous bulge in seven of our cases. One case was noted as having a marked protrusion: five months later the vitreous face was flat.

Another interesting finding was that in some cases the anterior hyaloid membrane has a double contour.

Condition of the Anterior Hyaloid Membrane

Previous observers are also agreed that tears and holes in the anterior hyaloid are often seen after intracapsular extraction, though exact percentages are seldom quoted. Leahey (1951) found such tears in 22% of cases; Irvine (1953) noted rupture of the vitreous face at a later stage in 23% of cases. Our findings (57 cases) were:

Intact	36 (63%) cases
One or two small holes with strands of vitreous in anterior chamber	17 (30%) „
Marked rents	4 (7%) „

In most cases there are one or two small holes: from these, loose strands and fibrils of vitreous project forwards into the anterior chamber. Sometimes numerous fine processes seem to spring from almost the whole of the anterior surface of the hyaloid. A large circular hole in the hyaloid membrane may also be seen. Through such a hole the vitreous herniates and forms a second condensation a short distance in front of the hyaloid membrane.

In one case only was there free vitreous in the anterior chamber without any demonstrable hyaloid membrane. In four instances small rents were noted which were later found to have disappeared. In two instances holes appeared in a previously intact vitreous face, as described by Irvine (1953) and Arruga (1956).

In those cases we examined in which alpha-chymotrypsin had not been used, the incidence of vitreous herniation and tears was almost the same as in the alpha-chymotrypsin series.

We do not think that the incidence of tears in the anterior hyaloid in this series is excessive, and we have no reason to believe that alpha-chymotrypsin helped to produce them.

Opacities in the Vitreous

Vitreous opacities occurred in 52 cases, as follows:

Small amount	15 (29%) cases
Moderate amount	26 (50%) „
Marked amount	11 (21%) „

In many cases wavy vertical lines, irregular tufts, and spots of opacity could be seen. These were mostly in the anterior part of the vitreous, which became more clear as one focused further back. The appearance is similar to that seen in myopia and old age. In only one instance did these opacities cause any interference with vision. It would seem that the trauma inflicted on the eye during a cataract operation leads to a degeneration of the vitreous with disruption of the normal framework and the appearance of opacities.

When we compared these cases with those in which alpha-chymotrypsin was not used there seemed to be a slightly higher incidence of vitreous opacities in the alpha-chymotrypsin group. We did not feel that the difference in this series of cases was too small to warrant any definite conclusions being drawn.

There appeared to be no increase over the period of the study in the amount of the vitreous opacities.

Posterior Detachment of the Vitreous

In both series of cases we found a high incidence of posterior detachment of the vitreous. We also noted the appearance of large optically empty clefts in the vitreous in several cases. Sometimes two or three of these clefts were present. We would postulate that when the lens is removed the anterior vitreous fills in the defect with the production of clefts in the vitreous itself or of a posterior vitreous detachment, or both.

Other observers have noted a high incidence of posterior vitreous detachment in older age-groups. Teng and Chi (1957) found a 44% incidence in the 50–80 age-group. Pischel (1953) found a 58% incidence in patients over 50 years. We think that there is an increased incidence of posterior vitreous detachment after intracapsular cataract extraction, but do not associate it with alpha-chymotrypsin.

Conclusions

We have no doubt that alpha-chymotrypsin weakens or destroys the zonule and makes cataract extraction an easier procedure.

There were no operative complications in the series that could be attributed to alpha-chymotrypsin.

The visual results compare favourably with our cases before the use of the enzyme and with the previously published figures of other authors not using alpha-chymotrypsin.

Only one severe post-operative reaction—the case of bullous keratitis—was not well explained.

There was some liberation of pigment from the posterior layer of the iris in about 50% of cases. This is probably mainly due to the mechanical effects of operative intervention. It does not seem to cause any harmful effect in the eye. We feel that it is more likely

to occur when using alpha-chymotrypsin but that this increase may be due to the slight increase in mechanical intervention.

There seemed to be a slightly higher percentage of cases showing increased opacities in the vitreous in this series than in our previous cases. We feel that the difference was not great enough for us to draw a definite conclusion. There was no increase in the amount of the opacities in any case during the follow-up period.

In our series the vitreous face was carefully inspected over a period of a year. The appearances were compared with earlier cases of our own and with the descriptions and statistics of previous authors relating to uncomplicated intracapsular extractions without the enzyme.

We believe that there is no greater tendency either to bulging forward of the vitreous face or to the appearance of rents and tears in the anterior hyaloid membrane when alpha-chymotrypsin is used.

There was no tendency towards deterioration in the vitreous face during the 12 months of the study.

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An exhibition of 1,200 British books on science, technology, medicine, and surgery has been assembled by the British Council for touring Japan early next year. This first large exhibition of its kind sent to Japan by the Council has been organized in collaboration with the Japanese Publishers' Association for Cultural Exchange. It is planned that the books will be exhibited first at the main universities of Tokyo and then in the principal university cities of Japan. There will be 33 sections in the exhibition covering all the main branches of science, technology, medicine, and surgery, and a 94-page catalogue listing each book has been prepared.

AETIOLOGY, DIAGNOSIS, AND TREATMENT OF PARAESTHESIAE IN THE HANDS*

BY

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This paper is primarily concerned with the syndrome of the carpal tunnel and the disturbance of median-nerve function arising therefrom. The clinical features, aetiology, diagnosis, and treatment of this condition are considered in relation to 327 patients under my care in the years 1948–58.

The term "acroparaesthesia" was introduced by Schultze (1893) to apply to a condition in which pain and tingling in the hands were the prominent features and in which physical signs were scanty or lacking entirely. Affecting women mainly, it tended to appear in middle life and most commonly between the ages of 35 and 55. In the next 50 years various theories were advanced to explain the symptoms of this disorder and varying therapeutic measures were advised—some rational, some bizarre—all having in common their relative inefficacy in relieving the symptoms of which the patients complained.

There are, of course, numerous conditions in which paraesthesiae may occur in the fingers, hands, and arms, usually as an incidental feature in association with other symptoms, and it was probably the recognition of the fact that paraesthesiae may at times result from the presence of a cervical rib that directed attention away from a possible distal mechanism.

Kinnier Wilson (1913) regarded the condition as invariably arising at the thoracic outlet and described two clinically distinct types—(*a*) that in which local wasting of the thenar eminence is pronounced, with paraesthesiae on the radial side of the hand, and (*b*) that in which generalized atrophy of the intrinsic hand muscles leads to a claw hand. He also described trophic and vasomotor changes and mentions the occurrence of gangrene of the index finger. Sargent (1921) reviewed 95 patients under his care in whom pain, paraesthesiae, disorders of circulation, affections of cutaneous and other forms of sensation, weakness, and wasting occurred in varying combinations. He mentioned the quite frequent absence of visible wasting in the muscles. Of 32 patients with muscle-wasting in the hands, 12 presented with wasting in the thenar muscles, and it is significant that operation on the neck often failed to relieve these latter patients.

Walshe, Jackson, and Wyburn-Mason (1944) and Walshe (1951) describe various mechanisms in relation to cervical rib, the first rib, the subclavian artery, and the clavicle, by which they consider acroparaesthesia may be produced. It is suggested that the localized wasting of thenar muscles may be due to a constant relationship of the fasciculi in the outer head of the median nerve to the subclavian artery—an observation that becomes untenable in the light of the work of Sunderland (1945) (see below). The same writers suggest that dilatation of the subclavian artery, with or without thrombosis and distal emboli, may play a part

*This study was carried out for, and was successful in, the South-west Metropolitan Regional Hospital Board's competition for research reports, 1959.

in the production of symptoms. Walshe states, however, that conservative treatment is usually unavailing and the results of scalene section are "not rarely negative."

The median nerve, by virtue of its situation on the volar surface of the wrist, is not uncommonly damaged by lacerations of the wrist—a type of injury quite commonly encountered in civilian life. It is now quite generally recognized that the nerve may be involved in closed injuries of the wrist and carpus. Paget (1863) refers to a patient at Guy's Hospital who sustained a fracture of the lower end of the radius "repaired with an excessive quantity of new bone." The median nerve was in consequence compressed, with resultant paralysis of the thenar muscles. The patient also developed ulcers on the tips of the index and middle fingers. The condition was cured by immobilization of the wrist in flexion. Watson-Jones (1926), in a paper on dislocation of the carpal semilunar bone, pointed out the frequent association of median nerve damage with this comparatively rare injury. Zachary (1945) described two cases treated by division of the transverse carpal ligament, in which bony deformity was associated with nerve injury. Cannon and Love (1946), in an account of "tardy median palsy," recorded 38 patients with signs of median nerve injury at the wrist; five had no deformity of the bone structure of the wrist or carpus. These writers draw attention to the common presentation with paraesthesiae and thenar atrophy.

Bailey and Carter (1955) described two cases of median-nerve palsy after acute infection of the hand. De Abreu and Moreira (1958) give an account of a patient who sustained a crush injury of the wrist, followed seven months later by pain in the thumb and index and middle fingers, leading to gangrene of the tips of these digits. The symptoms were relieved by division of the flexor retinaculum, and at operation the median artery was found thrombosed.

The fact that the median nerve may be damaged at the wrist without history or signs of external injury has received remarkably slow recognition. Putnam (1880) described 31 cases suffering from nocturnal paraesthesiae in the median territory. Marie and Foix (1913) described the case of a patient who, at post-mortem examination, displayed bilateral thenar wasting with the appearance of a neuroma of the median nerve at the wrist, and Hunt (1911) described three cases in which the lesion was theoretically localized to the flexor retinaculum.

Brain, Wright, and Wilkinson (1947) were probably the first to describe the carpal-tunnel syndrome, its clinical manifestations and surgical treatment. Kendall (1950) described 14 cases of median-nerve palsy arising at the wrist, and distinguishes the "spontaneous" carpal-tunnel syndrome from median palsy after prolonged direct pressure upon the palm. Since 1950 numerous papers on this subject have been written, among them those of Phalen (1951), Kremer, Gilliatt, Golding, and Wilson (1953), Reid (1956), Phalen and Kendrick (1957), Heathfield (1957), and Garland, Bradshaw, and Clark (1957). Further reference to the work of these writers is made in considering aetiology and treatment.

Paraesthesiae have long been recognized as a symptom of acromegaly, and there is now little doubt that they result from compression of the median nerve in the carpal tunnel. This is referred to by Woltman (1941) and Kellgren, Ball, and Tutton (1952).

More recently, Murray and Simpson (1958) have observed symptoms of the carpal-tunnel syndrome occurring in 26 out of 38 patients suffering from myxoedema.

Symptoms of Carpal-tunnel Syndrome

The cardinal symptoms of this disorder are paraesthesiae and pain mainly referred to the fingers and hand, numbness of the fingers, muscular weakness or clumsiness, muscular wasting, and trophic disturbance in the fingers.

Paraesthesiae

Predominantly nocturnal, paraesthesiae are by far the most common of the symptoms enumerated above and were the presenting symptoms in 313 (95.7%) of the 327 patients here considered. The remaining 14 made no complaint of sensory symptoms. Of the 313 patients, 118 (38%) complained of tingling at night only; in 17 (5%) tingling was diurnal only; and in 178 (57%) tingling occurred both by day and by night, but in all these latter the symptoms were much worse by night.

The description given was remarkably constant. Patients referred to the intense burning quality of the pricking sensation that roused them from sleep. Although this was often poorly localized, most of them describe the sensation as predominantly in the radial half of the hand, affecting particularly the middle finger, the index finger, and the thumb, the middle finger being the one most constantly affected. Many patients say that all the fingers are affected, but on being directly questioned, decide, often after some thought, that the little finger escapes. The tingling often radiates to the palm of the hand and occasionally to the wrist and lower part of the forearm. More frequently, however, the paraesthesiae occur distally and there is complaint of an aching pain felt at the wrist and sometimes proximally, extending well up the forearm, even to the elbow. While the tingling lasts, the tips of the affected fingers may be hyperaesthetic to light touch, and during this time a few patients have described how voluntary movement of the fingers requires a great effort of will—a condition probably analogous to "pseudo-cramp" that can be demonstrated in experimentally induced peripheral nerve lesions. Most patients describe the manœuvres that they adopt to obtain relief—hanging the arm out of bed, shaking the wrist, massage with the unaffected hand, walking round the room, bathing the hand with warm or cold water, and, commonly in female patients, making a cup of tea.

In the present series paraesthesiae were predominantly unilateral in 225 (72%), the dominant hand being affected in the great majority. The remainder had bilateral symptoms but the hands were seldom affected equally.

Diurnal paraesthesiae were seldom constantly troublesome, but tended to follow use of the hands, particularly in knitting, sewing, and writing. Less commonly they followed more massive use of the arm in carrying weights, gardening, scrubbing, wringing, and polishing. In general it was observed that the longer the history the greater was the likelihood of sensory symptoms appearing by day as well as by night.

A misleading feature of the sensory symptoms is the frequency with which complaint is made of pain in the arm, extending often to the elbow and sometimes even to the shoulder, in association with nocturnal paraes-

thesiae in the fingers. This phenomenon may occur when paraesthesiae are induced experimentally after the release of a pressure cuff on the arm or forearm. This is a symptom which has so commonly led to the erroneous diagnosis of "costo-clavicular syndrome" when in fact the trouble is occurring at the wrist.

Numbness of Fingers

Numbness of the fingers is a rather less common symptom, and, of those with sensory complaints, approximately 30% experienced some degree of numbness. Often varying in intensity, it affects most frequently the tips of the index and middle fingers, and the thumb less commonly. When present constantly it may constitute severe disability and cause clumsiness in the performance of fine movements—a disability which is, in fact, far greater than that produced by loss of the thenar muscles, even when the latter loss is severe. This is well demonstrated after surgical treatment; sensory recovery being the rule and motor recovery the exception. The ultimate disability is remarkably slight.

Muscle-weakness

A minor degree of weakness of the short abductor of the thumb was demonstrated in the absence of visible wasting in a high proportion (44%) of those with unilateral symptoms. (It is, of course, impossible to assess minor degrees of weakness when both hands are involved.) Severe weakness and wasting of the short abductor and opponens pollicis was present in 21% of the whole series. Fourteen patients (5%) presented motor symptoms alone, and most of these were men whose employment resulted in direct trauma to the palm of the hand.

Weakness and wasting are undoubtedly related to length of history, and neither was observed in any patient with a history of less than four months. All those with marked motor signs had histories extending over a year or more, and most of those with severe wasting had histories of at least five years' duration.

Trophic Changes

Severe cyanosis of the thumb and first and second fingers was observed in five patients. In two of these, symptoms could be related to known external trauma. Necrosis of the tips of the affected fingers had appeared in three. In two other patients intermittent pallor and cyanosis of the first and second fingers was present and closely resembled Raynaud's phenomenon. It was, however, induced by active use of the hand rather than by exposure to cold. A minor degree of trophic disturbance, presenting as an atrophy of the terminal pulp of the thumb, first, second, or third fingers, was quite common and was observed in 65 (20%) patients. Sever trophic change, like severe motor change, was related to duration of symptoms, and none of the five patients referred to above had histories of less than three years' duration.

Physical Signs of Carpal-tunnel Syndrome

The early records would suggest that acroparaesthesia is commonly present without associated physical signs. It is my contention that this lack of signs was more apparent than real and arose from the failure to undertake a really careful examination of cutaneous sensation on the fingers.

The physical signs present may be sensory, motor, or trophic, singly or in combination.

Sensory signs, as would be expected from the symptoms, are by far the commonest, and were present in 281 (86%) of the present series. The intensity of the sensory impairment varies within very wide limits, and, when present, was always confined to superficial sensation only, and for the most part it was possible to demonstrate only impaired perception of pain.

Most commonly it is possible to demonstrate impairment of perception of pin-prick over the volar surface of the two terminal phalanges of the index and middle fingers. Involvement of the terminal phalanx of the thumb is less common, and, when the ring finger is involved, loss is usually demonstrable on both the radial and the ulnar side. In no case was any disturbance of sensation found on the little finger, nor would such loss be expected, and in no case did loss of sensation extend beyond the distal transverse crease of the palm.

Loss of a demonstrable degree of thermal sensibility did not appear significantly, and impaired perception of light touch could be demonstrated only in those patients whose fingers were subjectively numb. Postural sensibility is never impaired.

Motor weakness, in the absence of wasting, is difficult to assess, but some degree of weakness appeared to be present in approximately 40% of patients. Most often this weakness will appear first in the short abductor of the thumb. The opponens pollicis is usually affected rather later and to a less degree.

Weakness is, of course, readily demonstrated when wasting is present. Wasting in its smallest degree is best observed by viewing the outstretched palm and digits from the lateral side. In this way quite a small degree of flattening of the thenar eminence may become obvious. More severe wasting is usually most marked in the short abductor of the thumb, the area of which muscle may ultimately become hollowed.

The disability from wasting and weakness of the thenar muscles is remarkably slight—the greater part of the disability arises from disordered sensation. This is clearly demonstrated after surgical treatment, when sensory recovery precedes motor recovery by weeks or months. This lack of disability must be ascribed to the unimpaired function of the long flexor muscles and interossei: when the former muscles are weakened by a median-nerve injury at a higher level, disability becomes very severe.

Tropic changes have already been described under "Symptoms," and further reference to them is made under "Aetiology."

Other signs have been described in the carpal-tunnel syndrome but have not been readily demonstrated in the present series.

Tinel's sign is said to be positive at the wrist in an appreciable number of patients by Phalen (1951) and Phalen and Kendrick (1957), who demonstrated this sign in 89% of 71 patients. I have never succeeded in inducing tingling by percussion over the wrist or palm.

Gilliatt and Wilson (1953) described a test in which they suggested that by cutting off the circulation in the arm by means of a cuff the patient's sensory symptoms could be reproduced. These writers distinguish between the paraesthesiae induced under such circumstances in normal sujects and those induced when "an irritative lesion of the median nerve in the carpal tunnel was suspected." In the latter case they found the induced sensory symptoms to be more severe

and mainly in the median-nerve territory. This finding was present in 24 out of 45 patients in one series described by Heathfield (1957).

I have carried out this manœuvre and was not successful in inducing specific paraesthesiae in any instance—a finding which is not unexpected when considered in relation to certain anatomical facts and physiological experiments referred to below. Tingling in the median territory was occasionally noted after release of the cuff, and this is more in keeping with the experimental work.

Other signs occasionally observed are deformity of the wrist from old bony injury or arthritis, and callosities on the palm at the site of habitual pressure from tools or instruments used occupationally.

In general, it may be said that the signs are predominantly sensory, in which case they are confined to the distal part of the median territory, that they are often very slight, but that careful examination will nearly always reveal some change.

Differential Diagnosis of Carpal-tunnel Syndrome

Once the frequency of this condition is fully realized its recognition seldom presents difficulty, but it must be borne in mind that paraesthesiae may also occur in the hand from other disorders of the central and peripheral nervous system. Among these, disseminated (multiple) sclerosis is probably the most common. In my experience, such symptoms appeared in 107 out of 235 patients with disseminated sclerosis and were the presenting symptoms of an attack in 89. In this disease the paraesthesiae tend to be light and continuous without particular relation to use of the affected limb and without special predilection for night-time. Sensory attacks of this kind are seldom of great duration and do not as a rule exceed two to three weeks. Some difficulty may arise in the absence of abnormal signs, but such is seldom the case, and the diagnosis is usually made clear by the presence of other symptoms and signs and perhaps by a history of previous episodes. Further, the dysaesthesia in this disease is usually of a wide distribution in the limb and is seldom, if ever, confined to the territory of the median nerve.

Symptoms arising in association with a cervical rib or the costo-clavicular syndrome should not give rise to much confusion in diagnosis, although hitherto a lesion in this situation has all too often been held responsible for symptoms which in fact arise at the wrist. A large number of my present cases had previously had treatment directed toward the neck and shoulders; two patients had had cervical ribs removed without benefit, and three had been subjected to scalene section with equal lack of relief. During the period under review, I have seen five patients in whom the diagnosis of costo-clavicular compression was made: four were subjected to operation for removal of an accessory rib and all four experienced some degree of symptomatic relief. The predominant symptoms were, in order of frequency, (*a*) vascular, with coldness of the affected limb and with typical Raynaud's phenomenon in three; (*b*) muscular wasting affecting all the intrinsic hand muscles—present in four patients; and (*c*) sensory symptoms and signs consisting of subjective numbness and objective disturbance of superficial sensation, the latter being present to some degree in all five patients and having a distribution corresponding to the first dorsal nerve root. Dysaesthesia at night was notable for its absence and its presence by day did not constitute a major symptom.

Cervical spondylosis may cause tingling in the fingers, but the associated symptoms will usually indicate the site of the disturbance. Notable among these are radicular pains—pain and stiffness of the neck. Selective weakness and wasting of the thenar muscles is very rarely seen in this condition. Disturbance of sensation, when present, is usually radicular in distribution and it does not correspond with the anatomical distribution of a peripheral nerve. Loss or reduction of a tendon reflex is not uncommon. *X*-ray examination of the neck may confirm the diagnosis, but it must be borne in mind that some degree of arthritic change is usual in subjects 50 years old or over, and in the great majority does not result in the production of symptoms.

The various forms of polyneuritis, both acute and chronic, are associated with signs such as loss of tendon reflexes and widespread motor and sensory changes, such as are never encountered in the carpal-tunnel syndrome.

Motor neurone disease may cause some difficulty in its early stages if the wasting should present first in the thenar eminences, but the absence of sensory symptoms and signs and the possible presence of fasciculation usually indicate the true nature of the condition.

It will be seen that the two disorders most likely to be confused with the carpal-tunnel syndrome are cervical rib and cervical osteoarthritis, but that the clinical manifestations of both are usually characteristic enough to prevent confusion arising.

Anatomical and Experimental Considerations

Sunderland (1945) has made a detailed study of the internal topography of the median nerve. He found that the nerve divides into its cutaneous and thenar muscular branches at an average distance of 37 mm. distal to the radial styloid line. The thenar muscles are innervated by a large branch containing one large funiculus and by a smaller branch containing two bundles. The bundle containing the digital cutaneous branch from the third interspace has the longest intraneural course. He found that the bundle groups of the terminal branches remain separate over the distal 50 mm. of the nerve. At a higher level the funiculi contain mixed fibres destined for many muscular and cutaneous areas. This observation would appear to make it most unlikely that any proximal lesion of the nerve could produce any consistent pattern of localized wasting in the hand.

Blunt (1959) has investigated the vascular anatomy of the median nerve in the forearm and hand by suitable injections of amputated limbs. He has shown that the median nerve below the elbow derives its blood supply from three main sources: proximally in the forearm from the median artery, by a branch of the ulnar artery just proximal to the flexor retinaculum, and more distally by branches from the superficial palmar arch. The latter branches course transversely just distal to the terminal gangliform enlargement of the nerve to give branches to the digital nerves, and continues with the nerve to the thenar muscles. Ascending branches arise from the same source and lie on the anterior aspect of the nerve and in the interfascicular connective tissue. These

branches anastomose with the branch from the ulnar artery, which latter also gives a branch to the common flexor sheath in the carpal-tunnel. The median artery arises from the common interosseous artery, the ulnar artery, or the anterior interosseous artery, and it seldom reaches the wrist.

The venous drainage of the nerve follows the arterial pathways.

Distal to the flexor retinaculum there is a marked increase of perineural connective tissue containing vessels of relatively large size. The surface vascular plexuses and the intraneural vessels run mainly in a longitudinal direction.

Blunt points out that there is nothing in the local vascular architecture to suggest that the median nerve is particularly liable to ischaemia at the wrist, but it may be relevant that in the carpal-tunnel the nerve lies in relatively avascular surroundings. The architecture of the nerve itself in its distal 3 in. (7.5 cm.) is highly fascicular and therefore resistant to compression. In this connexion Bentley and Schlapp (1943) have demonstrated that a peripheral nerve may be oxygenated by diffusion from surrounding tissues after occlusion of its nutrient vessels. The avascular nature of the carpal-tunnel may therefore be of singular significance.

Lewis, Pickering, and Rothschild (1931) studied the subjective and objective results of experimental lesions of peripheral nerves in man, and their results have been further studied by Weddell and Sinclair (1947). The latter writers observed two subjective responses, temporally distinct, that follow experimental compression of the arm with a cuff. They noted, first, a light tingling sensation perceived in the fingers when or shortly after the cuff is inflated, usually very brief and having a pleasant quality, and sometimes associated with a velvety numbness of the finger-tips. This phenomenon they call compression tingling. After release of the cuff a phenomenon referred to as release pricking appears, taking the form of a continuous tingling punctuated by sharp pricking sensation—the common "pins and needles." This is much more prolonged and persists for five minutes or more. They considered that compression tingling is produced at the site of the cuff and that release pricking may arise in any part of the limb, commonly at or near the peripheral nerve endings. The latter phenomenon they ascribe to the release of (unspecified) metabolites.

Other observations by these writers were: that compression at the wrist causes symptoms in the fingers only; that compression of the ulnar nerve without compression of major blood-vessels does not result in significant dysaesthesiae, and thence release pricking must bear a relationship to the state of the peripheral circulation.

Merrington and Nathan (1949), while mainly agreeing with the findings of Weddell and Sinclair, conclude that the symptoms induced by compression arise in the nerve trunks alone and not at the periphery. They produce convincing experimental evidence to support their contention.

It would appear, therefore, that symptoms having the character of those associated with the carpal-tunnel syndrome may be induced artificially by a cuff applied to the arm, and there is strong evidence to suggest that these symptoms arise from ischaemia of the nerve trunks. Can such experimental observations assist in elucidating the mechanism whereby the sensory symptoms of the carpal-tunnel syndrome arise?

It has been stated above that the median nerve in the tunnel receives its blood supply from above (from the ulnar artery) and below (from the superficial palmar arch) and these two sources anastomose in and around the nerve in the tunnel. It would therefore seem possible that a relative degree of ischaemia might arise from any cause which tended to reduce the blood flow either proximally or distally. In the absence of deformity, it is unlikely that internal bony compression or external compression could be operative factors. Two possibilities remain: the area of the nerve immediately proximal to the flexor retinaculum could be compressed directly by the surrounding tendons, thus interfering with the circulation at the point of entry of the branch from the ulnar artery, or the artery itself might be the subject of direct compression by muscle action. Of these, the former would seem the more likely.

Brain, Wright, and Wilkinson (1947) consider that the condition has an ischaemic basis and results from repeated dorsiflexion of the wrist. In support of this, they indicate that the available space for the median nerve in the tunnel is reduced by dorsiflexion of the wrist. Kendall (1950) considered that more dynamic factors were operative. He observed that the combination of slight dorsiflexion of the wrist with tension on the flexor tendons caused compression of the nerve at the wrist in the cadaver and that, with the wrist in this position, active contraction of the flexor tendons and of the palmaris longus tendon would tend to compress the median nerve between the two.

I support the view that compression of the nerve at the proximal border of the flexor retinaculum (with, of necessity, interference with its blood supply) by muscle action is the main factor in inducing the carpal-tunnel syndrome. This contention is supported in the present series by the striking absence of macroscopic abnormality within the carpal tunnel of the nerve or surrounding structures in the great majority of patients submitted to operation. A wide diversity of opinion has been expressed by various writers about the appearance of the median nerve at operation. Harris (1947) states that the median nerve is normally somewhat enlarged proximal to the tunnel. It is generally accepted that the normal nerve is flattened within the tunnel and that it spreads out into a reddish gangliform swelling at the lower margin of the transverse carpal ligament (see Piersol, 1930). It would seem not unlikely that "abnormalities" described at operation may be due to failure to recognize the normal changes in external configuration of the nerve as it passes from the wrist to the palm.

If ischaemia of the nerve can produce symptoms from pressure occurring proximal to the tunnel, a similar ischaemia arising distally and interfering with the blood flow to the nerve from the superficial palmar arch may account for those patients in whom the appearance of the carpal-tunnel syndrome can be directly linked with the use of tools habitually held firmly in the palm, such as chisels, screw-drivers, lathe handles, and the like.

A number of theories have been put forward to account for the fact that the sensory symptoms of the carpal-tunnel syndrome are so troublesome by night and, as a rule, so little noticed by day. Heathfield (1957) suggests that oedema occurs in the wrist structures by night and also suggests lying on the arm as a factor.

The latter is hardly tenable in those patients whose symptoms are bilateral. Osborne (1959) suggests nocturnal venous stasis as a cause. Others have suggested the nocturnal release of metabolites. All these theories overlook two facts: immobilization of the wrist by day will almost invariably relieve the sensory symptoms at night, whereas the use of night splints alone is usually without beneficial effect; secondly, there is a striking resemblance between the burning and the tingling of this disorder and the symptoms experimentally induced by release of a pressure cuff applied to the arm. It would therefore seem reasonable to suppose that the factors producing the symptoms by night operate by day, and that use or overuse of the wrist and fingers can produce a relative ischaemia, probably as a result of local swelling, and that release of this ischaemia takes place as the swelling subsides during the night's rest.

This contention is further borne out by the comments so frequently made by patients that they dare not knit or sew because of the knowledge that by doing so they will cause severe symptoms at night.

Aetiological Factors

Age.—The age incidence in the present series is set out in the Table.

Age:	20–30	31–40	41–50	51–60	61–70	70+
No.	17 (5·1%)	59 (18%)	94 (28·4%)	112 (35%)	42 (12·6%)	3 (0·9%)

It will be seen that the condition is most frequently encountered in the fifth and sixth decades.

Sex.—The majority of patients were women: only 20 (6%) men were seen with this condition.

Occupation.—Of the female patients, 96% were housewives, the majority doing no more than normal household duties. Four were part-time seamstresses, and among the remainder aggravation of symptoms by needlework was a very common complaint. The relationship of symptoms to physical activity was a clear one and patients commonly noticed that their symptoms lessened or even vanished on holiday or during enforced rest as a result of illness or operation. The appearance of symptoms occasionally coincided with the undertaking of new and unaccustomed physical activity. All the 20 male patients were doing heavy manual work: 12 were habitually using tools or machinery involving either a continuous powerful grip or repeated percussion in the palm of the hand.

Pregnancy.—Eighteen patients experienced the onset of symptoms during the latter half of pregnancy. Seven developed symptoms during the three months after delivery. No special significance can be attached to this, but it is obvious that increased finger activity (knitting, etc.) is likely in pregnancy, and extra work is also involved in the care of a young child.

The Menopause.—No particular connexion with menopausal symptoms was noted, although the maximum age incidence falls at the menopausal age. Young (1950) has postulated an endocrine factor in the production of symptoms in view of their not uncommon appearance in association with the menopause, pregnancy, and acromegaly. (Garland *et al.*, 1957) have suggested that fluid retention in pregnancy may be a factor.)

Bony deformity from old fractures with malunion and from arthritis of the wrist and carpus was present in 12 patients.

The right hand was affected three times as often as the left and the disorder was bilateral in 44 patients. In the bilateral cases the dominant hand was almost always the more severely affected.

It will be seen that the disorder is most common among "ordinary" housewives and that no common factor appears to be operative other than a normal degree of hard work.

Treatment

Two lines of treatment were adopted: conservative treatment, by means of which the affected limb was rested; and operative treatment, in the course of which the flexor retinaculum was divided.

The choice of treatment was decided by several factors, principal among which were the physical signs present. In general, all those patients in whom only sensory signs were present and those who displayed only a minor degree of motor weakness without wasting were treated conservatively in the first place. Secondly, the nature of the patient's work was considered: those intending to return to heavy manual work were more likely to experience relapse after conservative treatment, and many of these were submitted to operation without a trial period of rest.

All patients who showed definite muscle-wasting were advised to have surgical treatment, and the majority accepted this advice.

Various means of resting the wrist were considered and tried. Some degree of relief was often obtained by the wearing of a sling by day, but most patients succumbed to the temptation to use the hand.

Night splints of various kinds were tried, with uniform lack of success—patients treated in this way usually stated that they were obliged by their symptoms to remove the splints. It was therefore decided to use plaster-of-Paris to obtain more or less complete immobility of the wrist. Plaster was applied as for a Colles fracture, extending from the base of the thumb and leaving the fingers free. It was very soon found that the relief of nocturnal symptoms obtained in this way was so rapid and so complete that application of plaster could be used as a very reliable diagnostic test in cases of doubt. Frequently, relief of symptoms occurs on the night after application of plaster, and patients described quite dramatically how they had had their first peaceful night for weeks or months. The plaster was removed in all cases after 14 days. 173 patients (53%) were treated in this way, the results being as follows:

Symptoms relieved while in plaster-of-Paris	152 (88%)
Symptom-free after 2 months	123
" " 6 "	114
" " 18 "	89

Nineteen patients either failed to attend for follow-up or did not reply to a questionary. Reliable figures for a longer period have not been obtainable, but the inference to be drawn from failure of patients to attend or reply may perhaps be a favourable one.

The prolonged relief of symptoms after this procedure, in spite of return to normal activity, is interesting and possibly results from the fact that it was always explained to the patients that their symptoms had arisen from overuse; possibly thereafter they exercised extra care.

Forty-six patients who suffered relapse or whose symptoms were only partially relieved by immobilization of the wrist were subsequently treated surgically. All

but one were completely relieved, the majority within a few days of operation. The one patient was subsequently relieved by a second operation when it was found that the flexor retinaculum had not been completely divided.

Surgical Treatment

Although four surgeons were concerned in the treatment of patients in this series, the operative technique did not vary significantly. In all instances a longitudinal incision was made, extending distally from the wrist. In all cases the flexor retinaculum was divided throughout its length. No other surgical manœuvre was carried out. 116 patients were submitted to operation, and in nine of them bilateral operation was performed on consecutive occasions: it was not considered desirable that both wrists should be immobilized simultaneously.

In the great majority of patients no abnormality of the normal anatomical appearances was observed at operation. The exceptions were those patients in whom trauma had occurred in the palm of the hand in the course of their occupation. In these latter, marked thickening of the transverse carpal ligament was usually present, together with increased flattening of the median nerve in the distal part of the carpal tunnel.

The results of surgical treatment were entirely satisfactory. In only two patients was relief of sensory symptoms incomplete. Objective sensory changes may persist for a time after operation, the actual duration depending on the intensity of the pre-operative changes present. Objective change is usually undetectable after four to six months. Subjective sensory symptoms at night were rapidly relieved, usually prior to discharge from hospital (one to four days).

Motor recovery is very variable. When severe wasting is present, material recovery is not to be expected, but there is remarkably little disability from this. Minor degrees of muscle weakness and wasting usually disappear within three to six months.

Those patients whose work entailed the use of tools likely to press on the palm of the hand were subsequently supplied with sorbo pads to wear during working hours.

No case of keloid scar has been observed and no disability has arisen directly attributable to operation other than a minor degree of tenderness over the incision, which is usually short-lived. So far, no patient whose symptoms have been relieved by surgery has suffered any relapse.

Bilateral operation was not carried out on all patients with bilateral symptoms. It was usually found that after having the more severely affected side cured, the less affected hand improved spontaneously, no doubt because of the increased use made of the treated hand.

Recently, treatment with injection of hydrocortisone into the carpal tunnel has been advocated. I have no personal experience of this treatment, but have had referred to me nine patients so treated elsewhere, in none of whom had material benefit arisen. The rationale of this form of treatment is obscure: possibly the occasional association of the carpal-tunnel syndrome with such disorders as "tennis elbow" has led to its trial.

Summary

The carpal-tunnel syndrome comes within the category of minor ailments. Nevertheless, it is not only very common but is also a potential cause of much disability and distress, particularly as a result of its tendency to interfere with sleep. It is a condition which in the past has been all too commonly misdiagnosed and much time and effort have been directed toward treatment of the neck and shoulders in the mistaken belief that the symptoms are related to the "costo-clavicular syndrome." The concept of the latter as a common cause of peripheral paraesthesiae dies very hard. I have found, and still find, that the great majority of patients with the carpal-tunnel syndrome are sent to hospital for investigation of "cervical rib" or "costo-clavicular compression." It is also common to learn that patients have frequently been subjected to manipulation of the neck and neck-stretching with slings before the true diagnosis has become apparent.

Much time and distress could be avoided by the earlier recognition of this condition, and doubt may be readily dispelled by the simple diagnostic (and therapeutic) expedient of immobilizing the wrist in plaster-of-Paris.

While it is clear that the disorder is basically an ischaemic one, in which overuse of the wrist and hand plays an essential part, the exact mechanism by which this comes about is not entirely clear. From the available anatomical and experimental evidence, it seems likely that the blood supply to the median nerve in the carpal tunnel may suffer interference either proximally or distally, the former possibly by local intermittent swelling of a degree sufficient to interfere with the branch from the ulnar artery, the swelling or oedema occurring in the tendon sheaths or the carpal ligament or both.

In the case of the distal blood supply, this may suffer interference by direct pressure, externally applied, affecting the branches from the superficial palmar arch.

While there is still some difference of opinion with regard to the "normal" appearance of the median nerve at the wrist and in the carpal tunnel, there was seldom any convincing macroscopic abnormality in the majority of patients submitted to surgery in the present series.

In conclusion, it may be said that this condition, once diagnosed, is readily and satisfactorily treated and that the delight of the treated patient makes the disorder one of the most satisfactory of minor ailments encountered in neurological practice.

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FUTURE PLACE OF LUMBAR SYMPATHECTOMY IN OBLITERATIVE VASCULAR DISEASE OF LOWER LIMBS

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With the steady increase in the popularity of direct arterial surgery, in the form of grafting or disobliteration, the place of lumbar sympathectomy by itself in the treatment of obliterative vascular disease of the lower limbs is uncertain. It therefore seems worth while to consider the future status of this operation in the light of the results it achieves. The following observations are based on a review of 100 consecutive cases of obliterative disease followed up for between one and seven years (Table I) after lumbar sympathectomy. All the patients except two were traced, and follow-up examination was carried out personally on all the survivors.

TABLE I.—*Interval Between Operation and Review in 100 Consecutive Patients*

Interval in years	1–2	2–3	3–4	4–5	5–6	6–7
No. of patients ..	35	22	13	9	16	5

Note.—25 of the patients were dead and 2 untraced by the time of review.

TABLE II.—*Reason for Sympathectomy in the 100 Patients*

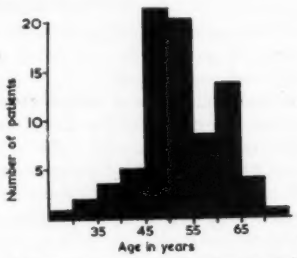
Ischaemic skin lesion or rest pain without claudication ..	14
,, ,, ,, ,, ,, with ,, ..	27
Uncomplicated claudication	59

The various reasons for operation are set out in Table II, and the results achieved are discussed under four headings: (1) sympathectomy and intermittent claudication; (2) sympathectomy and limb survival; (3) life prognosis after sympathectomy; and (4) the selection of patients for sympathectomy.

Sympathectomy and Intermittent Claudication

Intermittent claudication was complained of by 86 of the 100 patients. It is a predominantly male symptom, there being in the present series 6.6 males to each female. Contrary to the widely held belief that atherosclerosis is a disease of old age, the mean age at onset of the symptom was 52 years. Moreover, as illustrated in the Chart, there was a striking rise in the incidence after the age of 45. Indeed, claudication may be encountered in patients in their late twenties or thirties, and the early age of onset makes it a symptom of great importance.

Claudication is felt typically in the calf, this being the site in 93% of the patients who complained of it (Table III). Calf pain may be associated with buttock or thigh pain in patients with high arterial occlusions, and sometimes it is associated with pain in the foot. In only 7% of the patients was pain limited to the small muscles of the sole, which is perhaps surprising as these muscles are constantly in contraction during weight-bearing to assist in maintaining the longitudinal arch of the foot. By the time most of the patients were originally seen they were being forced to stop by the pain, and the claudication distance most commonly was 100 to 200 yards.



Age at onset of claudication in the 86 patients suffering from this condition.

TABLE III.—*Site of Pain in 86 Patients Suffering from Intermittent Claudication*

Site of Pain	No. of Patients
Buttocks, thigh, and calf	8
Calf only	60
,, and foot	12
Foot only	6

How Far Were the Patients with Intermittent Claudication Benefited by Sympathectomy?

Of the surviving non-amputated patients attending for review, 47 had been sympathectomized for claudication uncomplicated by skin lesions. These patients were therefore specially questioned about any improvement after operation. Twenty-one claimed that their claudication had been improved and 26 were emphatic that they had not been benefited in this respect. This suggests that a little under half the patients were improved by operation. However, more critical consideration of the 21 patients claiming benefit revealed positive improvement in only six, or 13%. A number of the patients who had claimed an increase in their walking distance admitted, on further questioning, that they had learned to walk much more slowly, and that if they walked as quickly as they had done before operation claudication pain came on as rapidly. Other patients did not claudicate after operation simply because claudication in the other leg, or anginal pain, forced them to stop before the pre-operative claudication distance for the sympathectomized leg was reached.

Blood-flow measurements, both at rest and in activity, and in limbs with normal and with occluded arteries, certainly give no support to the view that sympathectomy produces more than a transitory increase in muscle blood-flow (Grant and Holling, 1938; Wilkins and Eichna, 1941; Stein, Harpuder, and Byer, 1948; Shepherd, 1950; Dornhorst and Sharpey-Schafer, 1951; Duff, 1951; Barcroft, Dornhorst, McClatchey, and Tanner, 1952). The great difficulty in assessing the effect of treatment on such a purely subjective symptom as intermittent claudication lies in the fact that it is prone in its natural history to wide spontaneous fluctuations in severity. This is what makes the value of sympathectomy in the treatment or intermittent claudication such a

controversial subject, leading clinical authorities like Learmonth (1950) and Smithwick (1957) to hold opposing views on its efficacy. Even in the 13% of patients whose claudication had apparently been improved by sympathectomy, it is impossible to say to how great an extent the improvement was due to a spontaneous remission rather than to operation. Fortunately, to-day, direct attack on the diseased vessels will often permit more certain cure of claudication to be achieved. On balance, considering blood-flow studies and personal clinical experience, it seems that sympathectomy should not be recommended in the patient with uncomplicated intermittent claudication.

Sympathectomy and Limb Survival

Of the 100 patients, 41 presented with an ischaemic skin lesion or rest pain. Twenty-five of these also gave a history of intermittent claudication; but where cutaneous ischaemic change is present the primary aim of treatment is to prevent gangrene, and the success of treatment is dramatically demonstrated by the major amputation rate. In 55% of these patients the skin lesion healed after sympathectomy, and major amputation has not so far been required.

Selection of patients is the most important factor influencing the limb recovery rate after sympathectomy in those with skin lesions. If the foot, as distinct from the toes, is involved in frank gangrene, then amputation is inevitable whether or not a sympathectomy is carried out. When such cases are included in a series the amputation rate is high. If sympathectomy is restricted to patients with minimal digital gangrene, then the major amputation rate will be low. In the present series of 100 cases the overall major amputation rate was 15%, and it was 45% in the patients presenting with a skin lesion or rest pain. (The figure of 15% does not include two patients with unilateral sympathectomies who had a major amputation of their non-sympathectomized limbs.)

Limb Prognosis After Sympathectomy Related to the Pre-operative Clinical Course

There appear to be three distinct types of clinical course in relation to limb prognosis. Firstly, for example, of the 15 patients coming to a major amputation after sympathectomy for an ischaemic skin lesion, 11 required amputation within two months of sympathectomy, two more required it within five months, and in only two was the interval between the two operations more than a year. Of great interest was the fact that these patients coming to early amputation usually gave a very brief history prior to presenting with a skin lesion. Frequently there was no history of claudication. They therefore seem to have had a fairly acute type of illness, the clinical course being uninfluenced by sympathectomy and the limb progressing rapidly to gangrene. Edwards and Crane (1956) in their long-term follow-up studies noted that when amputation was required after sympathectomy it was usually required soon after. If a patient does not need amputation within six or so months of sympathectomy then he has a good chance of never needing it.

The second type of clinical course is that seen in patients with a long history of intermittent claudication who never develop a skin lesion. In none of the patients in the present series who were sympathectomized for uncomplicated claudication has a major amputation become necessary. It is impossible to say whether any of them would have come to amputation even had they not been sympathectomized.

Somewhere between these two clinical courses—the one leading to early amputation in spite of treatment and the other rarely leading to gangrene—lies a group of patients who give a long history of claudication but who at some time develop a minimal skin lesion. Often this is the result of local trauma. It is in this group of patients that lumbar sympathectomy might be expected to produce the best results, and in the present series they certainly fared best.

Measurements of blood flow, even in obliterative arterial disease (Gillespie, 1960), leave little doubt about the efficacy of lumbar sympathectomy in producing a lasting increase in blood flow in the foot, with protection from reflex vasoconstriction to environmental cold. This is likely to be of great importance in promoting the healing of existing skin lesions and the prevention of further ones. Certainly, the relief of rest pain by sympathectomy may be dramatic proof of the effect of operation.

The number of diabetic patients in this series was too small to allow them to be considered separately, but the greater incidence of skin lesions in diabetes is well documented and their limb prognosis is more grave (Edwards and Crane, 1956).

Life Prognosis After Sympathectomy

Obliterative vascular disease is rarely limited to the periphery, and these patients frequently have associated disease in the coronary or cerebral vessels which may be the cause of death at any time. Twenty-five of the 100 patients were dead by the time of review. The actual figure for the death rate in any series of patients, however, will greatly depend, as does the amputation rate, on selection of patients for operation as well as on the length of the follow-up period. If a high proportion of the patients in a series are sympathectomized for extensive skin lesions at an advanced age then the mortality will be greater than that in a series of younger patients operated on for uncomplicated claudication. Similarly, if diabetic patients are not included then the survival figures will be better.

However, even in the present series of cases, where a fairly conservative attitude towards sympathectomy for skin lesions in the elderly was adopted, the overall mortality of 25% within one to seven years of operation is strikingly high. Also, the mean age at death was only 57 years, and the mean survival time after sympathectomy just over two years (Table IV). There was no significant difference in the age at operation or at death between the 13 patients with a skin lesion or rest pain at the time of operation and the 12 patients operated on for uncomplicated claudication.

Cause of Death after Sympathectomy.—The cause of death in each of the 25 patients was ascertained (Table IV). Nine deaths were due to a cerebral vascular accident, seven to a myocardial infarction, and five either to a vascular cause or to bronchopneumonia after amputation. Only four of the deaths were from some cause unrelated to arterial disease, three being due to malignant disease and one to small-bowel obstruction.

Coexistence of Peripheral, Coronary, and Cerebral Artery Disease.—This and other reviews (Richards,

TABLE IV.—*Some Details of the 25 Dead Patients*

Interval between Operation and Death (Years)	Age at Death	Certified Cause of Death
13 Patients with a Skin Lesion or Rest Pain at Time of Sympathectomy		
1	65	Cerebral haemorrhage
4	75	Cardiovascular degeneration
3	59	Myocardial infarction
2	54	Cerebral haemorrhage
½	61	Small-bowel obstruction
1	64	Bronchopneumonia after amputation
½	52	Arteriosclerosis, diabetes, and pyelonephritis
½	52	Bronchopneumonia after amputation
3	65	Cerebral haemorrhage
1	58	Myocardial infarction
2	57	Cerebral haemorrhage
1½	74	,, ,,
1½	55	Myocardial infarction
12 Patients Sympathectomized for Uncomplicated Claudication		
5	69	Cerebral haemorrhage
2	52	Carcinoma of bladder and renal failure
3½	61	Myocardial infarction
1½	59	Subarachnoid haemorrhage
1	60	Bronchial carcinoma
3½	55	Cerebral haemorrhage
3	57	Carcinoma of rectum
1	56	Cerebral haemorrhage
1	67	Myocardial infarction
1	63	,, ,,
2½	42	Pulmonary embolus
5	51	Myocardial infarction

1957) have revealed a strikingly high incidence of coronary and cerebral artery disease in patients presenting with symptoms of peripheral obliterative vascular disease. 64% of the deaths in the present series were due to a coronary or cerebral vascular accident.

Evidence of coexisting coronary and cerebral artery disease was also sought in the 65 surviving non-amputated patients. Thirty-four of them, or 53%, had suffered a cerebral vascular accident or a myocardial infarction, had complained of angina, or had electrocardiographic changes suggestive of myocardial ischaemia (Table V). This close association of coronary

TABLE V.—*Evidence of Coronary or Cerebral Artery Disease was Present in 34 of the 65 Non-amputated Survivors*

	No. of Patients
Proved myocardial infarction and also cerebral haemorrhage	1
Cerebral haemorrhage	3
Proved myocardial infarction	11
Angina with E.C.G. evidence of ischaemia	6
Angina with normal E.C.G.	3
E.C.G. evidence of ischaemia, but no symptoms	10

and cerebral artery disease, with its attendant risk to life, must always be kept in mind when planning treatment, particularly extensive direct procedures in aorto-iliac obliteration. A patient with uncomplicated intermittent claudication is unlikely to lose his leg, but he has a high risk of coronary or cerebral artery disease.

Selection of Patients for Lumbar Sympathectomy

Consideration of the clinical progress of patients in this and other series, in association with the results of blood-flow measurements after operation already mentioned, allows certain conclusions to be drawn to assist in the selection of patients for operation.

Patients must first be divided into two groups, those with uncomplicated intermittent claudication and those with cutaneous ischaemia. As has already been discussed, intermittent claudication probably is uninfluenced by sympathectomy, so that operation should not be recommended in patients suffering from uncomplicated claudication. Patients with ischaemic skin changes seem benefited most by sympathectomy. While there has been no well-controlled series of cases reported in which sympathectomy has been compared with non-operative measures in the treatment of early gangrene, the measured effect of operation on cutaneous blood-flow, and the striking clinical improvement which so often follows operation, leave little doubt about its value. If direct surgery is not feasible in these patients —as so commonly it is not, owing to the distribution of the lesions, particularly in femoro-popliteal atherosclerosis—sympathectomy must be considered.

Not all patients with skin lesions are suitable even for sympathectomy, however. The progress of established gangrene in the foot itself will not be influenced by the operation, so that operation is unjustified. In less obviously unsuitable patients the clinical course of the disease so far will give some guide regarding the probable result of operation. Patients who present with a rapidly deteriorating foot, with a very short history, will probably progress to gangrene and amputation in spite of operation. On the other hand, those patients who develop a minimal skin lesion, such as a pressure ulcer or a small area of digital gangrene, in association with long-standing claudication, are likely to respond well. Blood-flow measurements support this view. It is therefore in this latter group that sympathectomy may prove most rewarding.

The prime indication for lumbar sympathectomy by itself in obliterative vascular disease is the early ischaemic foot in a patient who gives a long history of vascular trouble, but who, for one reason or another, is unsuitable for direct arterial surgery.

Summary

The clinical progress of 100 consecutive patients who had undergone sympathectomy one to seven years previously for obliterative vascular disease of the legs has been reviewed.

Only 13% of patients with uncomplicated intermittent claudication showed positive improvement after operation. How far this can be ascribed directly to the operation is discussed.

Over half the sympathectomies carried out in patients with ischaemic skin lesions were followed by healing of the lesion. The importance of good selection of patients in this group is discussed.

The association of peripheral, coronary, and cerebral artery disease was noted in a large proportion of the patients.

The indication for lumbar sympathectomy in obliterative vascular disease is defined.

My thanks are due to Professor D. M. Douglas for the interest he has shown in this work. Dr. H. Watson kindly interpreted the electrocardiograms. The review was assisted by a grant from the Scottish Hospital Research Fund, and was carried out in the Royal Infirmary, Dundee.

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ABO BLOOD GROUPS OF SIBLINGS OF DUODENAL ULCER PATIENTS

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Blood donors, prepartum women, and patients with disorders other than duodenal ulcer have been used as controls for investigations of the association of the ABO blood groups to duodenal ulceration. In a previous communication some of the reasons why the above are not entirely satisfactory controls have been pointed out (Buckwalter and Knowler, 1958). One serious weakness is that such random samples may inadvertently be selected from strata of the population which are not homogeneous with the patients, with skewed blood-type frequencies, thus invalidating their use as controls.

When siblings of duodenal ulcer patients are used as controls the possibility of racial stratification is eliminated. Since environmental and genetic variables are fewer, if a causal basis exists for the observed increased incidence of duodenal ulcer in persons of blood type O, stronger evidence of the association might be expected in families than in the general population. Data obtained from 293 duodenal ulcer sibships have been reported (Clarke *et al.*, 1956). These authors concluded that no evidence to support the hypothesis that a group O person is more likely to have a duodenal ulcer than his A, B, or AB sibs had been found. This is a report of a similar study, the results of which lead to somewhat different conclusions.

Methods

Since 1956 all patients seen at the University Hospitals with duodenal ulcer have become part of a continuing study concerned with the association of this disorder to the ABO and other blood groups (Buckwalter *et al.*, 1958). Patients from the Iowa City Veterans Hospital have been included since July, 1957. In approximately three-quarters of the patients the diagnosis is established at the time of operation; in the remainder there is a typical history of ulcer with a positive upper gastrointestinal *x*-ray study. A blood sample and relevant history is obtained from siblings of the patients (propositi). This is done at the University Hospitals or through the home physician.

In evaluating the data, sibs have been divided into those who have duodenal ulcer disease (affected), those who do not (unaffected), and those whose status is uncertain. There are among the unaffected sibs those with an occult ulcer at the time the information is collected. Information was insufficient in the uncertain group to permit their proper classification. Undoubtedly some of these sibs had duodenal ulcers. It is apparent that with the passage of time some of the at present unaffected siblings in the second and third groups will develop ulcers. These data and the results obtained when they are statistically evaluated, using the χ^2 method, are recorded in Table I. The differences which occur simultaneously in the four blood types were compared.

Results

The propositi (I) had the highest and the controls (V) the lowest blood type O frequencies. Note the high level of significance for the differences between the blood-type frequencies of propositi and controls. The blood-type frequencies of the affected (II), unaffected (III), and uncertain (IV) sibs all fell somewhere between the propositi and controls. When II, III, and IV are combined and compared with the controls, the differences are found to have borderline significance. No statistical significance is found for the differences between the propositi and sibs II and IV. The differences between the propositi and unaffected sibs likewise cannot be regarded as statistically significant. However, $0.05<P<0.10$ is interesting, clearly indicating the need for more data.

Clarke *et al.*, in analysing their data, used the method suggested by Dr. C. A. B. Smith, of the Galton Laboratory. Smith's method considers each family separately, thereby controlling the variable of family size. It has the great advantage that data obtained from separate studies may be added together and evaluated. Only families segregating for blood group including an O individual are used in this method; the details of the method has been described by Clarke *et al.* Of 480 sibships, 96 were found to segregate for O. In Table II are recorded the values for four representative segregating families, and the values obtained for all 96 sibships are added.

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TABLE I.—*Patient (Propositi) and Sibling Data; Results of Statistical Analyses*

Blood Type	I Propositi		II Affected Sibs		III Unaffected Sibs		IV Unknown Sibs		V Population Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
O	264	55·0	37	46·3	566	47·2	122	53·2	22,392	44·8
A	163	34·0	32	40·0	469	40·1	81	35·4	21,144	42·3
B	41	8·5	9	11·2	112	9·3	16	7·0	4,695	9·4
AB	12	2·5	2	2·5	39	3·4	10	4·4	1,748	3·5
Total ..	480	100·0	80	100·0	1,186	100·0	229	100·0	49,979	100·0

	χ^2	Probability
V compared with I	21·08	P<0·001
V " " II	1·05	0·10<P
V " " III	4·42	0·10<P
V " " IV	7·87	0·02<P<0·05
V " " I+II+III+IV	21·97	P<0·001
V " " II+III+IV	8·31	0·02<P<0·05
I " " II	2·31	0·10<P
I " " III	7·60	0·05<P<0·10
I " " IV	2·39	0·10<P

TABLE II.—*Analysis of the Chance of the Propositus Being Group O in the Sibships Segregating for Blood Group O*

Sibship No.	Total Sibs	Sibs Group O	Sibs Not Group O	Group O Propositi		Variance
				Observed	Expected	
608	6	2	4	1	0·3333	0·2222
3,437	3	2	1	0	0·6667	0·2222
6,280	5	3	2	1	0·6000	0·2400
7,383	5	2	3	1	0·4000	0·2400
In the whole series of 96 segregating sibships				56	46·9797	22·0082

From which we obtain $\frac{56-46\cdot9797}{\sqrt{22\cdot0082}}=\frac{9\cdot0203}{4\cdot691}=1\cdot92$. $0\cdot05<P<0\cdot10$.

TABLE III.—*Analysis of Combined Clarke and Iowa Data*

	Total Sibships	Group O Propositi		Variance
		Observed	Expected	
Clarke *et al.* ..	112	59	54·9095	25·8863
Iowa	96	56	46·9797	22·0082
Total ..	208	115	101·8892	47·8945

From which we obtain $\frac{115-101\cdot8892}{\sqrt{47\cdot8945}}=\frac{13\cdot1108}{6\cdot921}=1\cdot89$. $0\cdot05<P<0\cdot10$.

When these data are combined with those reported by Clarke *et al.* the results indicated in Table III are obtained. The number of propositi observed of blood type O are in excess of those expected in the Clarke and Iowa studies. However, the increased O frequency in the propositi is 1.92 times the standard deviation in the Iowa data, compared with 0.80 in Clarke's data. When the data are combined the difference in the observed and expected O frequencies of the propositi is 1.89 times the standard deviation (1.96, $P<0.05$). Additional sibship data (C. A. Clarke, 1960, personal communication) collected since 1956 is consistent. When this larger volume of data is combined with our data, $0.02<P<0.05$. Another advantage of this method of analysis is that it is not influenced by whether or not the sibs have ulcers. This is a possible source of error as noted before, since some of the siblings in the unaffected and uncertain group undoubtedly had peptic ulcers.

In 15 families there was an affected sib and segregation for group O. In Table IV are recorded sample data from such families, and the results of the analysis of the chance of the affected sib being group O. These data are combined and analysed with Clarke's in Table V. It will be noted that the observed frequency of blood type O in the Clarke and Iowa affected sibs was less than expected.

TABLE IV.—*Analysis of the Chance of an Affected Sib Being Group O in Sibships Segregating Group O and Duodenal Ulcer After Propositi have been Excluded*

Sibship No.	Total Sibs	Sibs Group O	Sibs Not Group O	Sibs with Ulcer	Sibs without Ulcer	Group O Ulcer		Variance
						Observed	Expected	
6995	6	3	3	1	5	1	0·5000	0·2500
7616	2	1	1	1	1	0	0·5000	0·2500
8315	4	2	2	2	2	0	1·0000	0·3333
In the whole series of 15 segregating sibships						8	9·9918	3·2832

From which we obtain $\frac{8-9\cdot9918}{\sqrt{3\cdot2832}}=\frac{1\cdot9918}{1\cdot812}=1\cdot10$. $0\cdot10<P$.

TABLE V.—*Analysis of Clarke and Iowa Data*

	Total Sibships	Group O Ulcer		Variance
		Observed	Expected	
Clarke *et al.* ..	14	6	6·9501	3·3594
Iowa	15	8	9·9918	3·2832
Total ..	29	14	16·9419	6·6426

From which we obtain $\frac{14-16\cdot9419}{\sqrt{6\cdot6426}}=\frac{2\cdot9419}{2\cdot577}=1\cdot14$. $0\cdot10<P$.

Discussion

The data presented provide qualified support for the hypothesis that the well-established increased frequency of blood type O among patients with duodenal ulceration has a causal explanation. Conversely, it makes the population stratification thesis even less tenable. Perhaps the strongest support for a causal hypothesis is provided by the comparison of blood-type frequencies of the propositi (I) and unaffected sibs (III) (Table I). Note that the χ^2 value is almost at the 5% level of significance. Assuming that these findings do indicate a group O ulcer factor, no satisfactory explanation can be offered at this time for the low O frequency of the affected sibs (II) or the high O frequency in the uncertain (IV) sibs. The comparatively small numbers, especially of the affected sibs (II), may be a factor. Another may be improper classification—that is, some affected (II) were really unaffected, while a substantial number of ulcers were actually present in the uncertain group.

The blood type O frequency is higher in all sibs as well as the propositi than in the controls (V). This is to be expected, since the siblings all come from a stratum of the population with a "built-in" high O frequency—namely, a "duodenal ulcer" population. This increased O frequency as compared with a "non-duodenal ulcer" population is dependent on the gene composition of the parents, and is not relevant to the duodenal ulcer group O association.

The findings are inconsistent with a maternal effect characterized by ulcer predisposition of all children whatever their blood type, as suggested by Clarke *et al.* A maternal effect leading to predisposition only or chiefly of O children is possible. It is possible, perhaps probable, that multiple factors which may be anatomical, immunological, biochemical, and/or enzymological, related to the genetic template, are responsible for the observed association of duodenal ulceration to the ABO blood groups.

The findings indicated in Tables IV and V are somewhat disturbing. Assuming a causal relationship, if the data are reliable (II, III) an observed O frequency higher than the expected would be anticipated in the affected sibs. The frequency of O in the affected sibs was actually lower than expected in both the Clarke and the Iowa data. At this time judgment concerning interpretation of these findings must be reserved. A total of 29 sibships provides insufficient data ($0.10<P$).

Conclusions

The sibship studies reported provide some support for the causative nature of associations between the ABO blood groups and duodenal ulceration. There is an indication for continuing these studies. It is urged that similar studies be undertaken.

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"PREMARIN" AS A HAEMOSTATIC AGENT: FAILURE TO DEMONSTRATE ANY LABORATORY OR CLINICAL EFFECT

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"Premarin" is a complex of oestrogen sulphates prepared from the urine of pregnant mares. During recent years it has been widely used as a haemostatic agent mainly in controlling epistaxis, but also in surgery, particularly on the prostatic gland.

Jacobson (1941) introduced the term "spontaneous bleeding," by which he understood any bleeding without a known cause such as trauma, surgery, tumours, ulcers, haemorrhagic diathesis, and so on. He believed this kind of bleeding to be a clinical entity, which was caused by a low oestrogen level in the blood, and postulated that premarin might arrest such bleeding.

The experimental support for the use of premarin as a haemostatic agent was offered by Johnson (1957). He injected premarin into 12 dogs, and 15 to 30 minutes later he found an increase in prothrombin and proaccelerin (factor V), and a decrease of antithrombin. The effect lasted for several hours. He concluded that "an elevation [of factor V] might be of importance for the prevention or control of bleeding. Should human plasma have a rise in Ac-globulin [that is, factor V] values following oestrogen administration proportional to that in the dog, this would be of unusual advantage to man."

During recent years several clinical reports have appeared, almost all claiming a favourable effect of premarin as a haemostatic agent. Apparently more than one million injections of premarin have been given, and no side-effects have been reported.

Jacobson (1954, 1955) reported that oestrogen therapy alone arrested bleeding in more than 300 cases of epistaxis, and in about 100 cases of various types of haemorrhages, particularly delayed post-tonsillectomy haemorrhage, rectal bleeding, gastro-intestinal bleeding, and subarachnoid haemorrhage. Menger (1955) reported a dramatic response to premarin in all of 16 cases of spontaneous epistaxis and haemorrhage after adenoidectomy. Rigg (1957), using premarin in ophthalmology and otolaryngology, stated that "there is no doubt in my mind that the amount of bleeding during surgery and the incidence of excessive bleeding post-operatively have been markedly reduced." Hall and Ursin-Holm (1959) found that premarin controlled the bleeding in 17 out of 26 patients with epistaxis and bleeding after tonsillectomy, and concluded that oestrogen therapy probably had an effect. Bleeker (1959) reported a striking effect in epistaxis and in surgery on the prostatic gland. Cooner and Burros (1960), in a double-blind study, could not demonstrate any haemostatic effect of premarin in prostatectomy.

We were asked by Nyegaard & Co., Oslo, Norway, to advise them whether premarin should be marketed in Norway. We felt that the theoretical concept of "spontaneous bleeding" was unsound, that the laboratory experiments could hardly explain the reported clinical effects, and that all clinical studies claiming good effect lacked adequate control groups. The following study was therefore undertaken.

Materials and Methods

Premarin, 20 mg. per phial, has been used for intravenous administration.

A placebo was prepared for intravenous administration by Nyegaard & Co.

Effect on the Haemostatic Mechanism in Normals.—In eight normal individuals (four men and four women) various tests on the haemostatic mechanism were carried out before and at intervals after an intravenous injection of 20 mg. of premarin. References to methods are given in Table I.

Effect on Abnormal Bleeding-time and Tourniquet Test.—The bleeding-time and the tourniquet test were tested before and one hour after intravenous injection of 20 mg. of premarin. The tourniquet test was performed according to the method of Stefanini and Dameshek (1955).

Effect on Blood Loss After Prostatectomy.—Thirty-one patients with benign adenoma of the prostatic gland who were operated on according to the method of Harris (1929) (Andersen, 1957) by the same team of surgeons, were given 20 mg. of premarin intravenously half an hour before the operation started. Twenty of them had another injection six hours after operation. The blood loss during operation and on each post-operative day was measured as haemoglobin in a Klett–Summerson photoelectric colorimeter and converted to millilitres of blood as the haemoglobin of the patient's blood was known. A sucker was used extensively at operation, and the blood was collected in the suction bottle. The contents of this bottle were diluted with distilled water

TABLE I.—*Effect of Premarin in Normals. Mean Value of Various Tests for Haemostatic Functions in Eight Normals Before and After 20 mg. of Premarin Intravenously*

	Before Premarin	After Premarin			Normal Range	Reference for Methods
		½ Hour	1½ Hour	3 Hours		
Whole-blood clotting-time (min.) ..	3½	3½	4	3½	2–5	Hjort and Stormorken (1957)
Bleeding-time (min.)	5	5	5½	5½	2–11	Borchgrevink and Waaler (1958)
One-stage prothrombin test (sec.) ..	14·7	14·8	14·6	14·7	13–15	Quick's test using human brain thromboplastin
Cephalin time (firm clot formed) (sec.)	57·0	57·9	58·3	57·3	50–60	Waaler (1957)
P and P test (%)	100	100	102	99	75–130	Owren and Aas (1951)
Prothrombin (%)*	100	99	101	98	75–130	Hjort *et al.* (1955)
Proaccelerin (factor V) (%) ..	100	102	104	104	70–140	Aas (1952)
Platelet count (×1,000 c.mm.) ..	248	254	240	246	150–350	Nygaard (1933)
No. of adhesive platelets (% of total)	41		44		30–60	Hellem (1960)

* Sensitive to Stuart factor (factor X).

to 10 litres for haemoglobin estimation. The swabs used were soaked in water, and the amount of haemoglobin was determined. The 24-hour urine was collected for each of three days, and haemoglobin was measured. This group of patients was compared with another group of 40 patients of the same age and with the same diagnosis, operated with the same technique, but without premarin therapy. Half of this group were operated on just before and half just after the premarin study. To the best of our knowledge the two groups were equal in all relevant respects, except for the premarin.

Effect on Epistaxis.—Eleven patients with severe epistaxis of more than four hours' duration, without hypertension and without haemorrhagic diathesis, were at random given either placebo intravenously or premarin 20 mg. intravenously. If necessary, the dose was repeated after one hour. Neither the patient nor the doctor knew whether the particular patient had received placebo or premarin.

Results

Table I shows the result of various tests for haemostatic functions in normals before and after premarin injection. Obviously no change took place within three hours after the injection.

Table II shows that 20 mg. of premarin intravenously had no shortening effect on the prolonged bleeding-time in patients with von Willebrand's disease or with thrombocytopenia of various causes. Nor did premarin twice daily for more than a week have any shortening effect on the bleeding-time in a patient with von Willebrand's disease (Table III). Table IV shows that a pathological tourniquet test remained unchanged after the injection of premarin.

Table V gives the results in prostatectomy. Mean, medium, and range have been recorded and no significant difference can be demonstrated between the groups. It is in fact more striking that the two groups are so similar. Blood transfusion was not necessary during operation, and only one patient, in the control group, needed 500 ml. on the second post-operative day.

Table VI shows the result of the small double-blind study in epistaxis. The placebo preparation was as effective as premarin in controlling the bleeding.

TABLE II.—*Effect of Premarin in Patients with Prolonged Bleeding-time*

Sex	Age	Diagnosis	Bleeding-time in Minutes		Platelet Count (per c.mm.)
			Before Premarin	1 Hour after 20 mg. Premarin Intravenously	
M	56	von Willebrand's disease	>30	>30	253,000
F	44	Cirrhosis	>30	>30	40,000
F	63	Pancytopenia	>30	>30	10,000
F	27	I.T.P.	30	28	78,000
M	33	Leukaemia	>30	>30	1,200

TABLE III.—*Effect of Premarin in One Patient with von Willebrand's Disease. Bleeding-time and Tourniquet Test in a 56-year-old Man Before and During Premarin Treatment, 20 mg. Intravenously Twice Daily*

	Before Treatment	Days on Treatment			
		5	6	10	12
Bleeding-time in minutes ..	>30	>30	>30	>30	>30
Tourniquet test, No. of petecchiae	20–30	15–20		20–30	

TABLE IV.—*Effect of Premarin on a Positive Tourniquet Test*

Sex	Age	Diagnosis	No. of Petecchiae	
			Before Premarin	1 Hour after 20 mg. Premarin Intravenously
M	56	von Willebrand's disease	15–20	30–40
F	63	Pancytopenia	30–40	25–35
M	33	Leukaemia	100–120	80–100

Discussion

Johnson (1957) found an increase in prothrombin, factor V, and a decrease in antithrombin after injections of premarin. It is not obvious to us that such an increase would be beneficial to patients. Patients with spontaneous bleeding are said to have normal coagulation (Jacobson, 1955), and there is no proof that an increased concentration of clotting factors leads to more efficient coagulation. Furthermore, if a hypercoagulable state were produced, it is not at all certain that this would be an advantage. Haemostasis in small vessels depends mainly on platelets and vascular factors, not on coagulation (Zucker, 1947). Therefore, hypercoagulability may not be able to stop diffuse bleeding. On the other hand, hypercoagulability may well be dangerous, leading to thrombotic processes and consequently a reduction in platelets, prothrombin, proaccelerin (factor V), and antihaemophilic A factor (factor VIII); in other words, an increased bleeding tendency might hypothetically be the result of the therapy. We admit that all this is speculation, but not necessarily less valid than the speculation which has been marshalled in favour of premarin.

Johnson worked with dogs, and we failed to confirm his results for prothrombin and factor V in man. Thus, if hypercoagulability is a useful therapeutic achievement, this argument can be valid only for dogs. Our findings have been confirmed by Nilsson (1960).

We could not demonstrate any effect of premarin in patients with haemorrhagic diathesis. This is, however, not surprising, since premarin is said to have effect only in "spontaneous bleeding," which excludes

TABLE VI.—*Cessation of Bleeding Within One Hour After One Injection (if Necessary Two Injections) of Premarin or Placebo into Patients with Epistaxis*

	No. of Patients	Cessation of Bleeding within 1 Hour	
		Yes	No.
Premarin	6	2	4
Placebo	5	2	3

TABLE V.—*Blood Loss in Prostatectomy*

	No. of Patients	Average Age	Blood Loss in ml.											
			During Operation			Rest of 1st Day			2nd Day			3rd Day		
			Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Without premarin ..	40	68½	122	104	24–286	127	95	16–508	61	43	8–200	52	37	6–258
Premarin*	11	70	123	122	30–222	124	112	42–258	67	39	18–164	52	34	10–174
Premarin†	20	67				131	68	8–425	57	42	8–168	51	26	0–266

* 20 mg. intravenously half an hour before operation. † 20 mg. intravenously half an hour before and same dose 6 hours after operation.

haemorrhagic diathesis as a cause of the bleeding (Jacobson, 1941).

Even if we could not show any effect on the haemostasis in normals, premarin might well act as a haemostatic agent clinically, through some as yet unknown mechanism. We chose to test this out in epistaxis and in surgery on the prostatic gland, two conditions in which the effect of premarin has been reported to be excellent.

We could not confirm the results of Bleeker (1959), who found that in prostatectomy the number of blood transfusions could be reduced by 50% when premarin was used. There can be no doubt that if premarin is given in surgery the evaluation of the effect should be done with a blind technique. If this cannot be done, it must be preferable to measure the actual loss of blood as in this study, rather than to rely on changes in haemoglobin values or impressions of the blood loss. There was no difference in blood loss between patients who received premarin, either preoperatively only or both pre- and post-operatively, and those who did not receive premarin. Our findings are in good agreement with the result of the double-blind study of Cooner and Burros (1960).

In this connexion we would like to point out that, according to Jacobson, "spontaneous bleeding" excludes surgical and traumatic bleeding. Therefore there should be no indication for premarin therapy in such cases.

Jacobson (1954) states that "spontaneous bleeding" is often preceded by tension or stress. One may assume then that the bleeding in itself will increase the anxiety and a vicious cycle will then be started. All kinds of treatment which would tend to break this cycle somewhere will reduce the actual bleeding. This should be kept in mind when the effect of premarin in epistaxis is evaluated. When a physician takes care of such a patient, talks with him, puts him to bed, gives him any kind of medicine, he will calm the patient and tend to break the cycle. This treatment in itself would be a major factor in controlling the bleeding. If premarin has any effect over and above this, it must be proved in a controlled study with a double-blind technique. This has never been done, and the clinical reports on premarin are therefore of little value in our opinion. Our double-blind study is unfortunately small, but it does suggest that the effect of premarin is only that of a placebo.

The theory that "spontaneous bleeding" is a clinical entity which is due to a low oestrogen level in the blood seems to us to be very speculative and loosely founded. So far as we know, this postulated low level of oestrogen has never been demonstrated. If the theory be correct, it is difficult to understand why there is not a striking difference in the incidence of spontaneous bleeding between men and women.

We have confirmed that premarin produced no side-effects. We think, however, that this fact in itself is no justification for the extensive use of premarin. We are afraid that such a drug will give the doctor who is using it a false sense of security, and that this, together with the additional expense, is against the best interest of the patient.

Summary and Conclusion

The haemostatic effect of premarin has been tested on: (1) various vascular, platelet, and clotting functions in normal individuals; (2) prolonged bleeding-time and positive tourniquet tests in patients with haemorrhagic diathesis; (3) patients undergoing prostatectomy: blood loss during operation and for the next three days has been measured, and compared with the loss in a control group; and (4) patients with epistaxis; in a double-blind study.

In the first three groups no effect, and in the fourth a placebo effect only, could be demonstrated.

Premarin produced no side-effects. Still, the danger of false security by using an ineffective haemostatic agent should not be underestimated.

As a result of this study, premarin has not been marketed in Norway.

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SCHOOLGIRLS' BEHAVIOUR AND MENSTRUATION

BY

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The possibility of girls' behaviour being adversely affected by menstruation has been discussed in a previous paper (Dalton, 1960), in which the deleterious effect of menstruation on school work was analysed. An excellent opportunity of studying their behaviour presented itself at an English public school. Here it is the custom for all order marks given for bad behaviour to be recorded together with the date and type of offence, and it is also customary for the matron to keep records of the girls' menstruation dates. This paper analyses offences committed during the spring term of 1960.

The school is situated in the Home Counties, occupies over 400 acres, and boards 350 girls between the ages of 8 and 19 years. The school aims to prepare girls "for the dual role of home-maker and professional woman, special attention being given to their moral and religious training." There is a preparatory school for girls between 8 and 11 years; the senior school is

divided into six houses each supervised by a housemistress and matron. This analysis deals with four houses only, records of menstruation dates being incomplete for the other two.

Method

Offences committed within 14 days before or 14 days after the onset of menstruation are the only ones included in this analysis.

The menstrual cycle of 28 days was divided into seven four-day periods, Days 1 to 4 represented menstruation and Days 25 to 28 the premenstruum. Offences committed during the 14 days before menstruation were allocated to the second half of the menstrual cycle thus:

1 – 4	days before menstruation	= Days 25–28
5 – 8	" " "	= Days 21–24
9 –12	" " "	= Days 17–20
13 and 14	" " "	= Days 15 and 16

This method of allocation eliminates the difficulty caused by the widely varying length of girls' cycles and is suitable for analysis of the effect of menstruation, premenstruum, and postmenstruum, but not for ovulation.

Results

During the 14 days before or after the onset of menstruation 272 offences were committed and of these 29% were committed during menstruation (Fig. 1). This is double the expected incidence had there been an even distribution of offences throughout the cycle. This same high incidence of offences during menstruation occurred among offences committed (*a*) during form time, (*b*) during free periods, and (*c*) administered by prefects; it persisted among individual offences and among those involving two or more girls, and it was not influenced by the regularity or irregularity of menstruation or by the duration of menstrual loss. Significance tests, using the χ^2 test with six degrees of freedom, show, in each instance, that the probability of such a distribution occurring by chance is less than one in a thousand.

The Table shows the preponderance of offences of various types during menstruation (the expected proportion for a purely random distribution being 14%). There is a significantly high proportion of offences committed during menstruation for unpunctuality, forgetfulness, and avoiding games. Talking was less significant as a menstrual offence, while eating during lessons and wearing the wrong clothes occurred evenly throughout the cycle.

Schoolgirls' Offences During Menstruation

Type	Offences During Menstruation		Total Offences	χ^2 on 1 d.f.	Probability
	No.	%			
All offences ..	82	30%	272	54·3	0·001
Unpunctuality ..	28	33%	84	25·0	0·001
Forgetfulness ..	6	43%	14	9·3	0·001
Avoiding games	7	37%	19	7·9	0·01
Talking	16	25%	63	6·3	0·02

The "good" girls with only one or two offences per term committed 26% of their offences during menstruation (as compared with the chance expectation of 14%), while the "naughty" girl with more than six offences per term was more influenced by menstruation, committing 36% of her offences during this four-day period (Fig. 2). The words "naughty" and "naughtiness" have been deliberately chosen as they are in common use at school, and avoid more serious associations of a term like "behaviour disorder."

Twenty-seven girls, who had committed more than four offences per term, were selected and the headmistress was asked to supply additional information about them—namely, whether they were above or below normal height, weight, or maturity; whether they were adopted or had any personal or home stress problems. These girls were grouped into three classes: (1) behaviour influenced by menstruation—that is, over 50% of their offences committed during menstruation; (2) behaviour possibly influenced by menstruation—that is, between 25% and 50% of their offences committed during menstruation; and (3) behaviour not affected by menstruation—that is, less than 25% of the offences committed during menstruation.

The headmistress was shown the three groups of girls' names, without knowing to which category they belonged, and was asked to comment on the groups.

The 13 girls whose behaviour was definitely influenced by menstruation were described as "just naughty from exuberance or laziness." Three had a personal stress—for example, broken home, ill parent—and their average intelligence was high, with only two in the lowest of

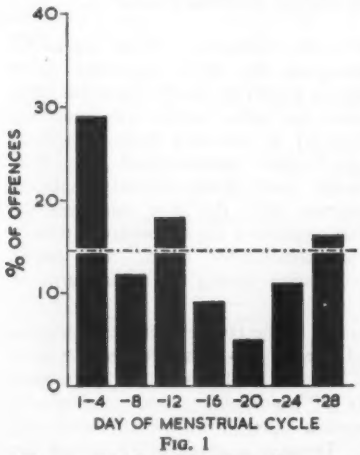

FIG. 1

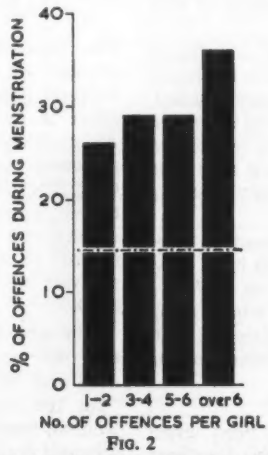

FIG. 2

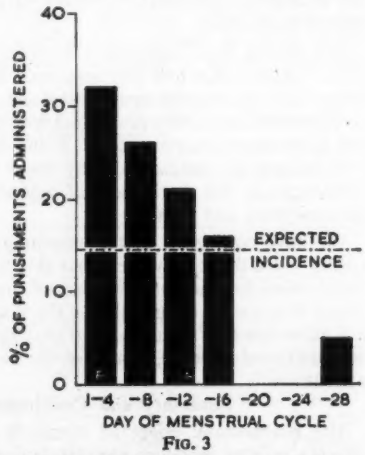

FIG. 3

FIG. 1.—Distribution of 272 offences committed during the menstrual cycle. FIG. 2.—Number of offences per term and those committed during menstruation. FIG. 3.—Punishment administered by prefects during their menstrual cycle.

the three academic forms for their age group. The commonest offences were lateness and talking.

The eight girls unaffected by menstruation were described by the headmistress as "problem girls requiring careful handling and understanding." Seven of the eight had a personal stress problem, one girl being described as "the most unfortunate girl in the whole school." Their general level of intelligence was below the average, and five of the eight were in the lowest form for their age. Disobedience and rudeness were the commonest offences in this group.

The intermediate group of six girls whose behaviour was possibly influenced by menstruation was correctly described by the headmistress as midway in characteristics between the other two groups. These girls were intermediate as regards the proportion of stress situations and the general level of intelligence.

This suggests that two types of naughtiness can be differentiated among schoolgirls. Firstly, naughtiness due to the hormonal changes of the menstrual cycle, which tends to occur among the brighter and well-adjusted girls. Secondly, naughtiness due to psychological stress, which is not affected by menstruation. The three groups were comparable with regard to height, weight, maturity, and size of families, but the group affected by menstruation tended to be younger, although not statistically significant.

There were 11 prefects among the sixth form girls, aged 16 to 18 years, who were permitted to punish girls for misbehaviour. An interesting and important feature is seen in Fig. 3 in that they gave significantly more punishments during their own menstruation, while their standards tended to rise at each menstruation and then fall gradually during the cycle. This raises the point whether the same is true of women generally, especially teachers, magistrates, and others in authority.

Summary

In schoolgirls there is a significant increase in misbehaviour during menstruation, particularly offences such as unpunctuality, forgetfulness, and avoiding games. The offences during menstruation are especially increased among naughty girls.

Two types of naughtiness could be distinguished. Firstly, that occurring predominantly during menstruation. These girls were free from psychological stress and tended to be the more intelligent. Secondly, that occurring evenly throughout the cycle, in girls with recognized psychological problems.

The administration of punishments by the prefects is significantly influenced by menstruation.

I thank the headmistress for permission to analyse her books, and for her kind co-operation in all stages of this investigation; Dr. P. Armitage for his statistical advice; and Dr. E. W. Dunkley for his wise criticism of the script.

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An Institute of Thoracic Diseases has been established at the Royal North Shore Hospital, Sydney, Australia. The aim is to model the Institute on the Institute of Diseases of the Chest associated with the Brompton Hospital and the London Chest Hospital, and as it develops it is hoped to organize extended courses to which Asian students will be welcome. (*Med. J. Aust.*, October 1, 1960.)

HYDROPS FOETALIS WITH A FAST-MOVING HAEMOGLOBIN

BY

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The clinical picture of hydrops foetalis is well known, and the most important cause of this disease is thought to be incompatibility between the mother's blood and the foetal blood.

During a study of the haemoglobin of premature and stillborn infants we came across a premature infant who clinically showed the symptoms of hydrops foetalis, with hepato-splenomegaly and anaemia, and who carried an unusual fast-moving haemoglobin in the blood. This case drew attention to the possibility of a faulty haemoglobin metabolism as another cause of this well-known clinical picture.

Case Report

A married woman aged 24 was admitted to hospital because of vaginal bleeding during pregnancy. She was about 34 weeks pregnant. This was to be her second child. Her first child, a boy, was born prematurely at the age of about 36 weeks. After about two weeks in hospital she was delivered of a premature female infant by breech, who showed gross abnormalities. The infant was hydropic, weighed 2,630 g., and had a body length of 42 cm. Oedema was marked and generalized. The child looked anaemic. The head appeared relatively small, while the extremities were rather short. The spleen and liver were greatly enlarged. The placenta looked very abnormal. It was greatly enlarged and very thick and oedematous. Its weight was about 2 kg., and it was anaemic and friable. On microscopical examination Dr. Sutomo Tjokronegoro, professor of pathology, found that the stroma of the chorionic villi was oedematous and loose, with here and there hyperplasia of the stroma cells. The capillaries contained numerous normoblasts and erythroblasts, of which many were young (see Fig. 1). The picture was compatible with that found in cases of erythroblastosis foetalis.

Routine haemoglobin analysis carried out on the cord blood showed it to be unusual. By the paper electrophoretic method of Smith and Conley (1953), at *p*H 8.6, two haemoglobin spots were seen. One had the mobility of haemoglobins A and F, while the other was a fast-moving haemoglobin which was much faster than normal haemoglobin A but definitely slower than haemoglobin H. At *p*H 6.5 it was more anodal than haemoglobin A, but more cathodal than haemoglobin H, and had the same mobility as haemoglobins Fessas and Papaspyrou (1957). It could easily be distinguished from haemoglobin J at this *p*H, because at *p*H 6.5 haemoglobin J did not separate from haemoglobin A, while the above-mentioned component was clearly separated from haemoglobin A. It is a pity that we did not have available for comparison the Bart's haemoglobin, which was described by Ager and Lehmann (1958) as migrating between haemoglobin A and haemoglobin H and as being slightly faster than haemoglobin J and haemoglobin Fessas and Papaspyrou. The unusual

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component in our hydropic infant formed the major component (see Fig. 2), contrary to what has been found up to now in all of the cases of newborn infants carrying a fast-moving type of haemoglobin (Lie-Injo, 1959). The amount of alkali-resistant haemoglobin examined by the method of Singer *et al.* (1951) was found to be 44.3% of the total haemoglobin.

Unfortunately, no haematological study of the blood could be done, as the infant, which died shortly after birth, was taken away by the family. However, the numerous

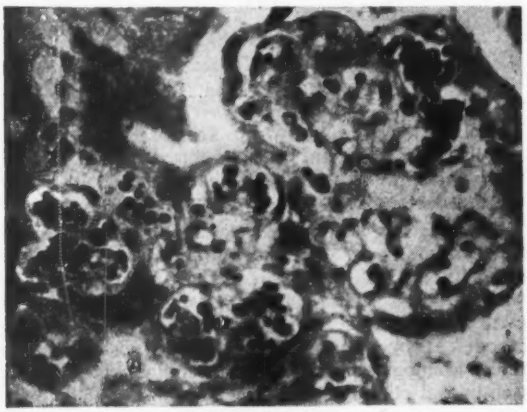

FIG. 1.—Capillaries of the chorionic villi in the placenta filled with nucleated red blood cells, many of which were young.

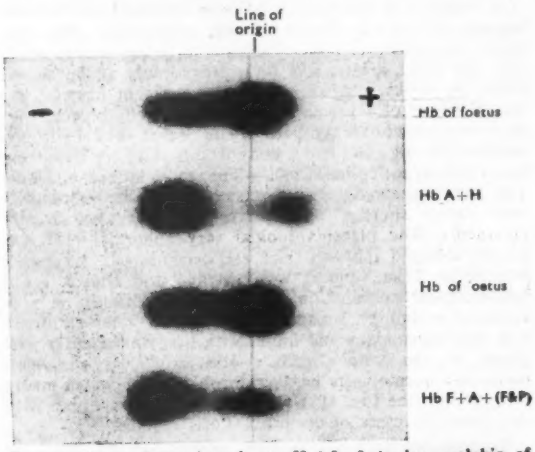

FIG. 2.—Paper electrophoresis at *p*H 6.5 of the haemoglobin of patient with hydrops foetalis compared with Haemoglobin H and Haemoglobin Fessas and Papaspyrou (F and P). Note the large amount of unusual component in the foetus with hydrops.

normoblasts and erythroblasts present in the capillaries of the foetal placenta indicated that there was severe erythroblastosis of the foetal blood.

Both parents were physically normal except that the mother looked slightly anaemic. The spleen and liver in both parents were not enlarged. Study of the blood of the mother revealed that she was of blood group A, N, Rh positive, genotype CDe/CDe. No abnormal circulating antibodies and no potent anti-β haemolysin could be found in the mother's blood. The Wassermann and Kahn reactions with her blood serum were negative. One month post-partum she had a slight anaemia of 10.6 g./100 ml., which was clearly microcytic and hypochromic. The red blood cell count was 5,660,000/c.mm., P.C.V. 38%, M.C.V. 67.1 cubic microns, M.C.H. 18.7 $\mu\mu$g., M.C.H.C. 27.9%. The number of reticulocytes was 0.2%. The resistance of the erythrocytes to hypotonic saline solutions was slightly increased. No pathological haemoglobin could be detected in her blood, while the amount of alkali-resistant haemoglobin was within normal limits.

The father was of blood group B, MN, Rh-positive, genotype CDe/cDE. He had no anaemia, his haemoglobin being 14.8 g./100 ml. However, there was a clear microcytosis and hypochromia. The red blood cell count was 7,250,000/c.mm., P.C.V. 50%, M.C.V. 69.0 cubic microns, M.C.H. 20.4 $\mu\mu$g., M.C.H.C. 29.6%. The reticulocytes were not increased. The resistance of the erythrocytes to hypotonic saline solutions was slightly increased. Also, there was no pathological haemoglobin in his blood. The amount of alkali-resistant haemoglobin was within normal limits.

We were not allowed to examine the first child in this family, who was 11 months old.

Comment

From the above findings it seems possible that the hydrops foetalis with accompanying severe anaemia, hepato-splenomegaly, and erythroblastosis of the foetal blood was not caused by antagonism between the mother's and the infant's blood, leading to the formation of antibodies against the infant's erythrocytes (extracorpuscular factor), but that it was caused by a faulty haemoglobin metabolism (intracorpuscular factor), leading to excessive destruction of erythrocytes, and this again leading to the symptoms found in the foetus and in the placenta, which closely resembled those found in hydrops foetalis caused by antagonism between mother's and infant's blood. If so, this is a new and interesting aspect of the problem of hydrops and erythroblastosis foetalis, and is deserving of further study.

We would like to thank Professor Sutomo Tjokronegoro for permission to quote his findings; Dr. Lie Hong Gie for his interest and co-operation; and the nurses of the obstetric department of the Jang Seng Ie hospital for their kind help.

ADDENDUM.—Since the completion of this communication we have been able to obtain the Bart's haemoglobin by the courtesy of Dr. H. Lehmann and Dr. J. A. M. Ager, of London. We found that the fast-moving mass of haemoglobin had the same mobility as Bart's haemoglobin. Whether a small amount of haemoglobin H was present could not be established with certainty.

In the meantime we have found three other severe cases of hydrops and erythroblastosis foetalis associated with the same fast-moving haemoglobin. Two of these cases were twins. That the greatest part of the fast-moving pigment in these cases was Bart's haemoglobin was confirmed by Drs. Ager and Lehmann. In addition, a small amount of haemoglobin H was present in these three cases. Meanwhile, Dr. Fessas has reported that he is of the opinion that Bart's haemoglobin is identical with his original Fessas and Papaspyrou type of haemoglobin (*Brit. med. J.*, 1959, 2, 886).

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"It ought to be more widely known than it is, that in this country the yearly number of registered deaths from suicide alone is 5,000; this exceeds the numbers due to pulmonary tuberculosis or road accidents." (Professor Martin Roth at London Medical Exhibition, November 14.)

TREATMENT OF STATUS ASTHMATICUS BY HYPNOSIS

BY

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Cases of asthma occurring for the first time in later life are often severe and progressive. The case is described of a man of 60 who appeared to be dying in status asthmaticus. His condition fulfilled the definition of status asthmaticus as "a condition in which the attacks become continuous with little or no remission by day or by night and do not appear to respond to any form of therapy" (Boland, 1952).

In this patient, since the onset of his asthma at the age of 54, it had become increasingly severe and was resistant to all physical therapy. As a final resort hypnosis was tried and was found to cut short the attack instantaneously.

Case Report

A man aged 60 was admitted to hospital as an emergency case on November 7, 1958, with a six-years' history of asthma and gradually increasing breathlessness on exertion. The family history revealed asthma in his sister and his daughter. Over the past year he had suffered from mid-sternal pain on exertion, relieved by rest, nocturia, and swelling of the ankles. For two days before admission his asthma became increasingly severe, having been precipitated by foggy weather.

On examination he was found to be obese, very cyanosed, severely dyspnoeic, with continual wheezing and a productive cough. Sputum was greenish yellow and contained many pus cells. Numerous coarse rales were heard in all areas of the chest. Pulse rate 100 a minute, blood-pressure 148/90; otherwise no physical abnormality could be found. *X*-ray examination of chest showed increased shadowing of right basal area suggestive of a recent inflammatory process. The lungs were emphysematous with some prominence of the hila, indicating chronic bronchitis. E.C.G. normal. Hb, 100%; W.B.C., 13,800 (60% polymorphs, 37% non-segmented—no increase in eosinophils); film normal; E.S.R., 12 mm.

After treatment with penicillin, 500,000 units q.i.d. aminophylline intravenously and oxtriphylline ("choledyl") 20 mg. q.i.d., slow improvement occurred. The bronchospasm took about a week to settle and the sputum became mucoid. He was discharged home on December 7 on a maintenance dose of oxtriphylline 200 mg. q.i.d.

He was readmitted to hospital on March 16, 1959. Since his discharge he had continued to be very breathless, particularly during the night, waking up with severe wheezing attacks.

On examination he was again in severe orthopnoea, continually wheezing, with numerous sibilant rhonchi and crepitations at both bases. There was mild cyanosis. Hb, 94%; W.B.C., 13,000; E.S.R., 36 mm. *X*-ray examination of chest showed some emphysema.

Progress

A rigorous regime of antibiotics, intravenous aminophylline and oxtriphylline was given together with physiotherapy. There was no improvement. Intravenous aminophylline was required overnight but gave little relief. Aminophylline suppositories were similarly tried without success and the patient gradually became worse. Noradrenaline spray, intermittent oxygen administered by mask, and adrenaline given three-hourly failed to bring relief. On April 19 A.C.T.H. gel, 80 units daily, was started, but by now status asthmaticus had supervened and he was no longer relieved by any of the treatments tried.

On April 21 I was consulted as a last resort in order to try hypnosis. When seen the patient was deeply cyanosed and was wheezing and gasping for breath; he was propped up in bed, with his chest kept in maximum inspiration and moving little, almost unable to speak and no longer able to move about. It seemed likely that he would die unless his bronchospasm was relieved. In these unfavourable conditions hypnosis was tried.

The usual technique was used of relaxation, eye fixation, and suggestions of sleep. The patient, however, was unable to relax, requiring all his accessory muscles for breathing. He was in a severe panic state, saying continually: "The end is near, doctor; the end is near." After simple explanation, stressing the importance of co-operation, hypnosis was started, being induced with surprising rapidity. Within 10 minutes a deep somnambulistic trance (Davis and Husband) developed. The suggestion was given, "Now you will find the wheezing stops and your breathing becomes free and easy." The wheezing stopped instantaneously. On sounding the chest almost no bronchospasm could be detected and within a few minutes the patient began to regain his colour. On waking he showed considerable surprise and began to cry, saying: "I have not felt so easy for five years." He then went to sleep for most of the day. Hypnosis was reinforced on alternate days for 10 days, and for the first time in years the patient was able to sleep throughout the night without any wheezing. He was taught how to induce hypnosis in himself, and began to control his asthma attacks by counting slowly to 10 and relaxing consciously. At the end of 10 days he became elated, which may well have been a steroid effect, and danced a jig in front of the ward patients to illustrate how fit and well he felt. At this point he was discharged home.

Psychiatric History

He appeared to come from a happy home, and his early childhood and school years had been uneventful. Throughout his life he had been a most successful man, building up his own business and later becoming sales manager to a large firm. He was happily married and had a son and a daughter. He had lost his son three years previously of coronary thrombosis at the age of 36. This was a great loss to him, but his asthma did not appreciably worsen at the time. The asthma had been incapacitating enough to prevent his working for the previous nine months. Only during the last few weeks had he become apprehensive about the future. In summary, he was a most capable, successful man of stable personality, suffering from severe asthma occurring in later life, with evidence of constitutional predisposition.

Discussion

Response to Suggestion

This fact of response is now well known (Asher, 1956; Fry, 1957; Kennedy, 1957; Stewart, 1957; Mason and Black, 1958). In this case *two* components may well have been relieved simultaneously.

The Panic State.—The patient was in a severe panic state, believing himself to be dying. Because of this he did not use his accessory muscles economically. The advent of a new therapy and the suggestions given may have contributed greatly to the relief of this panic. It is a common observation that in status asthmaticus the distress is often out of proportion to the actual bronchospasm present, and in many cases it is probable that death would not occur if the patient kept his head (A. Kennedy, personal communication).

The Bronchospasm.—This was very severe. Its relief may have been directly due to the effect of suggestion or, alternatively, to a reduction in the panic experienced by the patient. It is difficult to be sure which factor operated here. A direct effect on bronchospasm, how-

ever, is suggested by the observation that wheezing continued when he had already become relaxed. When a definite suggestion was given that the bronchspasm should cease, it immediately did.

Clearly, hypnosis appears to draw on some unknown and, as yet, untapped reserve which acts as powerfully as any drug known, but with none of the disadvantages of drug administration. This is demonstrated in other conditions where hypnosis appears to be able to induce a biophysical change in an organ (Sinclair-Gieben and Chalmers, 1959). In the present case hypnosis produced an instantaneous release of bronchospasm where all other measures had failed. It is likely that simultaneous reduction in the panic state may have led to the more economic use of the accessory muscles. Certainly, breathing deepened and the patient was able to lie down and breathe with less effort.

In spite of the terrifying nature of status asthmaticus, the prognosis is usually good, except in the elderly and in those with cardiac damage. Sooner or later the attack appears to "break," particularly where steroid therapy has been administered. The possibility exists, therefore, that the end of his attack was near and that hypnosis only provided sufficient relief to tide him over until this point was reached.

On the other hand, this patient was known to have angina pectoris, and therefore the outcome of his status asthmaticus might well have been fatal. It is felt, therefore, that hypnosis can be said to have had important therapeutic influence.

Is Asthma an Illness Determined by Psychological Factors?

Studies have indicated that individuals suffering from bronchial asthma may possess distinctive personality characteristics, including a disproportionately large number of symptoms. (French and Alexander, 1941; Fine, 1948; Miller and Baruch, 1948, 1957; Abramson, 1954; Linford Rees, 1956; Dekker and Groen, 1956; Fitzelle, 1959.) Harris (1955) and Harris and Shure (1956) draw attention to the *impossibility* of establishing the independence of emotional factors in the aetiology of the ailment, because of the traumatic nature of the symptoms.

The present patient seems to have been a well-adjusted individual, who had been successful in the three major spheres of human activity—work, marriage, and interpersonal relationships. Similarly there were no signs of psychiatric breakdown; neither was there evidence that he used neurotic mechanisms to deal with stressful life situations.

It is widely believed that conditions responding to hypnosis must of necessity be wholly psychologically determined. However, in other conditions—for example, organic pain, warts—it has been demonstrated that hypnosis can influence an accepted physical disease entity. The relief of bronchospasm by hypnosis in this case, therefore, does *not* necessarily provide further evidence in favour of a purely psychological basis of asthma.

Ease of Trance Induction

In many respects this patient could not have been more unfavourable for the induction of hypnosis. Aged 60, extremely anxious, gasping for breath, and unable to relax, yet he proved to be easily hypnotized.

All those who practise hypnosis are struck by the vagaries of trance induction. This varies not only from patient to patient but from one day to the next in the same person. In this case hypnosis was probably successful because of the patient's desperate condition. He knew this was his last chance and was determined to take it. Failure of hypnosis has often been observed to be related to deep-seated anxiety. On the other hand, White (1941) found that motivation does play a part in determining hypnotic susceptibility. In this case the patient's motivation may have overcome all other unfavourable factors.

Summary

A case is described of severe status asthmaticus in a man of 60 who was apparently dying. His condition responded dramatically to hypnosis. Theoretical implications are discussed.

Final Note.—A few days after discharge the patient died suddenly of acute heart failure. At the time there was no wheezing or bronchospasm, and his asthma had been minimal since discharge. Permission for post-mortem examination was not obtained, and the cause of death was not firmly established.

I thank Professor W. M. Millar for his helpful criticism; Mr. G. Sharp for his advice; Professor H. W. Fullerton for his kind permission to publish this case; and the late Professor Alexander Kennedy for his help in the preparation of this paper.

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At a recent meeting of the medical advisory panel of the London Amateur Boxing Association Dr. J. L. BLONSTEIN gave an account of the medical arrangements at the Olympic Games boxing contests in Rome. There had been 293 competitors and 274 contests. The boxing contests had lasted for 12 days and some boxers had five or six contests during this period. Boxing sessions were held at 3 p.m. and 9 p.m. Some boxers went into the ring between 1 and 2 a.m. and did not get back to the Olympic village until 3 a.m. Boxers with cuts of the head and face were allowed to box on and go forward to the next heat. In 274 bouts only once did a referee consult the doctor about a cut eye. There were other cases of cut eyes and overt injuries which the referees ignored. A member of the medical jury gave an opinion on his own compatriot and allowed him to box on with a cut eye. Doctors were not always available in the treatment rooms. Many boxers drank out of the same cups and flasks, and the same sponge soaking in a bucket of water was passed from boxer to boxer. Many of the boxers were novices and might have received serious injuries if they had met the very experienced boxers taking part. It was a mistake, in Dr. Blonstein's view, to hold the Games in Rome in August. The heat was a great handicap to the British boxers, who did well to win three bronze medals.

Reviews

TROPICAL SURGERY

Surgery and Clinical Pathology in the Tropics. By Charles Bowesman, O.B.E., B.A., M.D., F.R.C.S.Ed., F.A.C.S., D.T.M.&H.Ed. (Pp. 1,068+viii; illustrated. £5 10s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

The practice of surgery in the tropics not only includes every branch of surgery, but also demands a special knowledge of some aspects of surgery and of various surgical conditions rare or unknown in a temperate climate. Many of the standard textbooks fail to emphasize how far-reaching the effects of the special conditions may be. The surgical problems peculiar to the tropics are seldom discussed in sufficient detail. This book sets out to bridge this gap. The author, who has spent most of his surgical career in Africa, is a keen observer who has been at pains to record his observations and willing to learn from his mistakes. He has written a book primarily for the assistance of medical officers who are called upon to undertake all branches of surgery under conditions where facilities may be limited. The subject-matter is presented on a non-specialized basis, and throughout the emphasis is on simplicity and practicability.

The influence that tropical conditions can have on the presentation of disease, on differential diagnosis, and on surgical management is well described. The special surgical problems resulting from tropical disease are carefully reviewed. Throughout the bibliography is excellent. The earlier chapters deal with the effects of the special conditions on common surgical problems. Nutrition, fluid balance, and anaemia are discussed against this background. Under conditions where liver disease and gastro-intestinal disturbances are so common, it is odd to find no mention of vitamin K in the section on nutrition, and no account of heat stroke, its prevention or treatment, in that on fluid balance. There is a fascinating account of sickle-cell anaemia which is full of valuable advice for a surgeon working among Africans or people of African extraction. The chapter on the helminthic infections is also very valuable, but it is a pity that the medical aspect of treatment is dealt with in such detail, as many of the drugs described have now been superseded. The accounts of both schistosomiasis and amoebiasis are thoughtful, painstaking, and thorough. In stressing the importance of recognizing schistosomiasis as a generalized disease the presentation has perhaps become a little unbalanced. The reviewer would have liked to see a more detailed description of the management of the more commonly encountered genito-urinary complications of this disease. In an excellent account of portal obstruction, hypertension, and ascites there is a most helpful résumé from the Egyptian literature of those methods most likely to be successful in dealing with these conditions when due to schistosomiasis. In the account of amoebiasis the author gives the impression that he advocates operative measures for amoebic liver abscess. This in the opinion of the reviewer is rarely required for a right lobe abscess. It would have been helpful to include detailed advice on the diagnosis and management of amoebic typhlitis and of acute appendicitis complicating amoebiasis.

Gastrectomy is accepted as the surgical treatment for peptic ulceration, but it is perhaps unwise to recommend this operation for perforated gastric ulcer unless the operation is undertaken by an experienced surgeon. There is useful advice for dealing with large herniae, but it is a pity that in this section there is no mention of the McEvedy operation for femoral hernia. The advice on sigmoidoscopy is unsound: to advocate the passage of the instrument into the sigmoid colon with the introducer in position is most unwise. This examination should always be carried out under direct vision. Aperients and special preparations are also only very occasionally necessary. Much valuable data may be lost by routine preparation of the patient for this examination.

It is difficult for a single author to produce an up-to-date textbook, and it is unavoidable that minor inaccuracies should appear. These and a tendency to repetition are the only faults to be found in a well-produced book which fills a long-felt need. The author is to be congratulated on assembling a great deal of material not to be found in existing textbooks and on writing a book which will undoubtedly prove of great value to those practising surgery in the tropics.

H. R. I. WOLFE.

PRACTICE IN THE TROPICS

Differential Diagnosis for Practitioners in the Tropics. A Clinical Handbook. By W. H. Jopling, M.R.C.P.(Lond.), M.R.C.P.(Edin.), D.T.M.&H.(Eng.), in collaboration with Sir Philip Manson-Bahr. (Pp. 159; illustrated. Issued free of charge.) London: FBA Pharmaceuticals, Ltd. 1960.

The practice of medicine in the tropics basically is the same as that of medicine anywhere else; "tropical medicine" is only an addition to it, and it is erroneous to consider it preponderant. The practising physician working among the indigenous populations of the warm countries has to deal with a vast range of conditions; usually he has to do so without professional contacts, much less specialist advice, and remote from laboratory services and hospital facilities. He is dependent on his own knowledge, his own senses, and the simple equipment he can carry with him for the diagnosis of the disorders he encounters. His difficulties are augmented by the fact that he has to deal with backward peoples who are governed by superstitious beliefs and live under conditions favouring a multiplicity of complicating diseases and troubles.

With these facts in mind the authors of this small volume have compiled in small compass a surprising amount of information relevant to its title. This information is presented in the form of notes, with elaborations where deemed desirable. Virtually the whole field of medicine, in its widest aspects, is covered. The approach is essentially clinical; it is directed to the examination of the patient and the possible interpretations of the observations made during simple clinical examination. At the end of the book there are tabular appendices indicating how the clinical diagnosis can be substantiated by laboratory and similar investigations, where these can be undertaken. In its slender form, with excellent illustrations, this booklet should prove of much value to those for whom it is intended—practising doctors in the tropics.

A. R. D. ADAMS.

HYGIENE IN THE TROPICS

A New Tropical Hygiene. By Leonard Goodwin, M.B., B.S., B.Pharm., B.Sc., and Anthony Duggan, M.D., D.T.M.&H. Illustrated by Ian T. Morrison, M.A. (Pp. 148. 5s. 6d.) London: George Allen and Unwin, Ltd. 1960.

The advancement of hygiene in the developing countries of the tropics depends largely on health education, which achieves its best results when directed towards children. There is, therefore, a need for books for children which explain in simple terms how their bodies function and how communicable disease spreads from person to person. The book reviewed here has been designed for pupils in the top forms of primary schools, for middle schools, and for elementary teacher-training colleges. It has been written primarily for African students, but it would prove useful in any part of the tropics.

After two introductory chapters the first half of the book has thirteen short chapters on the anatomy and functions of the different systems of the body. The second half is concerned with the nature and manifestations of disease, together with brief descriptions of the common diseases of the tropics. These are grouped according to their epidemiology, and an account is given of the main control measures used. The book ends with two chapters dealing respectively with poisonous insects and snakes, and with "healthiness." There is an excellent index.

This book admirably achieves its object. The language is simple, and homely metaphors are used which should be comprehended easily by any child in the tropics. The essential information is given clearly and not obscured by detail. Numerous excellent diagrams and drawings illustrate the text. The authors are familiar with tropical diseases and conditions, and they have succeeded in compressing into 135 pages of text that will interest a child the information which they intended to impart. This is a book which can be strongly recommended for use in schools in the tropics.

T. H. DAVEY.

PAEDIATRIC ANAESTHESIA

Anesthesia for Infants and Children. By Robert M. Smith, M.D. Foreword by Robert E. Gross, M.D. (Pp. 418; illustrated. 90s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

As in most branches of medicine, anaesthesia is tending to split up into a number of sub-specialties. The thoracic anaesthetist talks of things unfamiliar to his plastic colleague. Both might feel reluctant to undertake difficult neurosurgical or obstetric cases. The paediatric field is now becoming another of these subdivisions of anaesthesia, in which special problems must be solved for successful surgery.

Whatever may be said deploring this fragmentation of medicine, at least those who work within the fragments do become expert and intimate with their field to an extraordinary degree. Dr. Robert Smith is internationally known for his skill in anaesthetizing children and infants for the many and intricate surgical operations in these patients. His book is outstanding because he achieves his objective, clearly aimed at, of setting down his accumulated experience as a practical anaesthetist. Here are no pseudo-erudite embellishments to frustrate the clinical reader, but only an ample, detailed, and helpful account of practical paediatric anaesthesia. The scientific basis of Dr. Smith's methods is constantly emphasized, and authorities in the physiological and allied fields are freely quoted and reproduced; all are wholly relevant to the clinical theme. In short, it is refreshing to read a modern textbook on clinical anaesthesia in which the central figure, dominant throughout, is the patient. Of the contents, one need only say that they encompass every possible nook and cranny of the subject, from the physiology and psychology of the infant to the legal aspects of paediatric anaesthesia, and from minor surgery to the most complicated of open heart operations. All are dealt with on a basis of personal experience.

The book is a delight to handle. Binding, paper, and the large number of illustrations are of the highest standard. It will be a long time before Smith's book is displaced as the standard work on anaesthesia for children.

W. W. MUSHIN.

NUTRITIONAL ENCYCLOPAEDIA

The Heinz Handbook of Nutrition. A Comprehensive Treatise on Nutrition in Health and Disease. Executive Editor: Benjamin T. Burton, Ph.D. (Pp. 439+ix. 45s.) London, New York, Toronto: McGraw-Hill Book Company, Inc., for H. J. Heinz Company. 1959.

The editorial board responsible for this useful book is made up of six of America's leading nutritionists, F. S. Daft, Grace A. Goldsmith, Helen A. Hunscher, C. G. King, W. H. Sebrell, and F. S. Stare. The subject matter covers a wide range, with several chapters each on the utilization of foods, the food elements, nutrition in health, nutrition in disease, and additional aspects of human nutrition. A wealth of information is supplied in readily available form. Some of the numerous tables list important foods and give their content of the better-known nutrients. Other tables deal separately with each of the less familiar nutrients, and list the foods which are their richest sources. Thus information is given about nutrients which are not mentioned in most conventional food tables, such as pyridoxine, folic acid, vitamin B_{12}, pantothenic acid, biotin, copper, zinc, manganese, and fluorine. Structural formulae of the vitamins are included, but there are no illustrations to show the effects of malnutrition. No references are made to original publications, but it would obviously be impossible for so much information to be included in a book of reasonable size without this sacrifice. The reader must depend on the expert knowledge and discretion of the distinguished authors, and can do so with confidence.

The chapters on nutrition in disease, including diabetes, diseases of the gastro-intestinal tract, malabsorption disorders, liver diseases, cardiovascular diseases, renal diseases, gout, osteoarthritis, congenital metabolic disorders, anaemias, neurological and psychiatric disorders, and skin diseases, are commendable for the valuable practical advice which they contain. In subsequent editions, however, more attention should be given to the index, which seems inadequate in relation to the mass of information which is provided. Thus no entries can be found for either bread or cheese, two very important foods which are mentioned in the text. Another minor criticism may be directed against occasional instances of verbosity, which sometimes obscure the meaning. An example may be taken from the introduction: "Since a slight degree of empiricism is almost unavoidable in dietotherapy, only the most convincing evidence was used for guidance in the presentation of special diets." Some readers, of

course, may grasp the meaning of these words at once, but others may be left in doubt, even after reading the sentence several times. Even those left in darkness on this point, however, will not fail to appreciate the solid virtues of this excellent publication, both as a textbook and as a nutritional encyclopaedia.

T. MOORE.

TEACHING INTELLIGENT ANALYSIS

Principles and Methods of Clinical Chemistry for Medical Technologists. By Eugene W. Rice, Ph.D. (Pp. 286+xvii; illustrated. 56s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

In his preface the author states that his intention is to teach the student laboratory technician to apply his training in basic chemistry so as to perform his analyses intelligently rather than mechanically, an aim which would receive the whole-hearted approbation of all directors of hospital biochemical laboratories.

The first seven chapters are devoted to laboratory mathematics, the basic principles of analytical chemistry, volumetric analyses, colorimetry and photometry, choice of methods, and control of accuracy and precision. The purpose of analyses of various components of blood, digestive juices, cerebrospinal fluid, urine, and faeces is described in the next four chapters, which are followed by a short discussion on toxicology. The remaining half of the book is devoted to technical procedures, many of which have been recently introduced.

It is difficult to appreciate the type of person to whom this book is directed, for the level at which the various sections are treated is very variable. One would expect even the rawest of technical recruits in a British laboratory to be familiar with the metric system, logarithms, equivalent weights, and standard solutions. These elementary subjects are all included, but much of the sections on basic principles is rather superficial and many of the terms used are inadequately defined. This criticism also applies to the chapters on body fluids, where the reader encounters several medical terms which may be new to him. It is doubtful whether many readers of this book would be capable of tackling toxicological analyses and such complicated procedures as the estimation of serum iron or protein-bound iodine. The reviewer was surprised to read that in infective hepatitis the highest transaminase levels are reached two to three weeks after the onset of the disease.

The author must, however, be commended for making a serious attempt to introduce the idea of checking the reliability of analytical results, and for providing certain key references to the original literature. Despite its shortcomings this book might well assist many aspiring technicians.

J. H. WILKINSON.

PROBLEMS OF RESUSCITATION

Problèmes de Réanimation. Journées de Réanimation Médico-Chirurgicale, Nancy, April 25–26, 1959. Compte-rendu de Rapports, Communications et Discussions. Edited by Professor P. Michon and Professor A. Larcan. (Pp. 405; illustrated. NF. 30.) Paris: G. Doin et Cie. 1959.

The *Problems of Resuscitation* is an account of the papers and discussions at a medico-chirurgical meeting held at Nancy last year. A wide range of fields is covered in the four sections. In the first part of the book the subjects are those associated with metabolic acidosis and alkalosis. The causes and treatment of hypokalaemia and hypochloraemia are discussed in one paper; respiratory derangements are described in another, and diabetic acidosis is considered in another; and the use of laevulose in acidosis is reported. The second part is devoted to the acid–base equilibrium in respiratory states such as artificial ventilation, tracheotomy, asthma in infants, and salicylate intoxication. In the third part there is a discussion of acute delirium. Finally, in the fourth part the subject is acute and extensive haemorrhage, its treatment, and the complications of the various treatments. Ten short independent papers come at the end. The subjects are well chosen and clearly set out.

It is altogether an interesting and instructive survey of the thought and work in France on these matters at the present time. Some papers have full bibliographies. The type is good and the illustrations are clear.

TERENCE EAST.

AMERICAN HISTORIES

Public Health in the Town of Boston, 1630–1822. By John B. Blake. (Pp. 278+x; illustrated. 52s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959.

The Massachusetts General Hospital, 1935–1955. By Nathaniel W. Faxon, M.D. (Pp. 490+xv. 80s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959.

Boston has for long been regarded as pre-eminent for its literary institutions and libraries, while Cambridge four miles distant is the seat of Harvard University, the oldest university in the United States. The town and University early fostered science and medicine, and, thanks to the writings and influence of Dr. Henry Viets, Dr. Edward D. Churchill, and others, several interesting medical histories and biographies of their eminent physicians and surgeons have already appeared. The two works here considered add to this increasing store of knowledge.

Dr. Blake has made a special study of the public health history of Boston from 1630 to 1822 when the town became a city. He shows that malnutrition, epidemic infections, and kindred disorders were more inimical to the early settlers of America than hostile Indians. The Pilgrims, for instance, lost half their company through disease in the first winter. He traces the development of public health practice in Boston from haphazard emergency measures to a systematic organization for the prevention and control of certain epidemic diseases. Much of the book is concerned with the combating of smallpox, and the inoculation and vaccination controversies are narrated at some length. Smallpox was a menace during the revolutionary period. Measures for combating yellow-fever epidemics are also fully described. It is to be hoped that in another volume Dr. Blake will carry the history of Boston's public health further.

The Massachusetts General Hospital was founded in 1811 and is famed throughout the world. From the outset its founders recognized that care of the sick must be associated with teaching; and since 1912 a third function, that of medical research, has been added. In chronological order this is the fifth volume of the hospital's history. Nathaniel I. Bowditch, a trustee, wrote of the first forty years (1811–51); the Rev. G. E. Ellis, a trustee, continued the story to 1872; Mrs. Grace W. Myers, librarian of the Treadwell Library, surveyed the years 1872 to 1900; and Dr. Frederic A. Washburn, director, the years 1900 to 1935. Now Dr. Faxon, director emeritus, has ably brought the history up to

1955. These twenty years were both stimulating and impressive. The hospital, formerly housed in a single building, is now a group of 14 major buildings and many smaller ones; there have been great developments in provision and facilities for research, while the hospital's early association with the Harvard Medical School has grown to include many disciplines and nearly a thousand students annually.

Here are given an evaluation of the contributions of women's organizations; chapters on anaesthesia, radiology, the "tumor clinic," and the blood bank; accounts of the problems evoked by the second world war, by disease epidemics, and by a disastrous fire. Dr. Faxon also writes an interesting excursus on the history of the hospital apothecaries.

These two books, naturally, have a special appeal to Bostonians and to persons who have been connected with that city and with the Massachusetts General Hospital. They will also be appreciated by those interested in public health, medical and hospital history generally.

ARTHUR S. MACNALTY.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

V. Babes: Opera Alese. Volume III. (Pp. 278.) Bucharest: Editura Academiei Republicii Populare Romine. 1960.

Conferinta Nationala de Fiziologie. July 1960. Rezumatele. Comunicarilor. (Pp. 176. Lei 7.25.) Bucharest: Editura Academiei Republicii Populare Romine. 1960.

Mental Health and Social Policy 1845-1959. By Kathleen Jones, Ph.D. (Pp. 237. 28s.) London: Routledge and Kegan Paul. New York: The Humanities Press. 1960.

Addendum 1960 to the British Pharmacopoeia 1958. Published under the direction of the General Medical Council. Official from March 1, 1961. (Pp. 83+xxi. 30s.) London: Pharmaceutical Press. 1960.

Medical, Surgical, and Gynecological Complications of Pregnancy. By the Staff of the Mount Sinai Hospital, New York City. Edited by Alan F. Guttmacher, M.D., and Joseph J. Rovinsky, M.D. (Pp. 619+x; illustrated. £6 12s.) London: Baillière, Tindall and Cox, Ltd. 1960.

Insuricienta Cardiaca. By I. Enescu. (Pp. 114. Lei. 4.50.) Bucharest: Editura Academiei Republicii Populare Romine. 1960.

Intraspinal Tumors of Childhood. By Robert W. Rand, M.D., Ph.D., and Carl W. Rand, M.D. (Pp. 560+xvii; illustrated. £6 12s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Cirrhosis of the Liver. By Martin Seler Kleckner, jun., A.B., M.S. in Internal Medicine, M.D. (Pp. 729+xix; illustrated. £9 16s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Pharmacology of Anesthetic Drugs. A Syllabus for Students and Clinicians. By John Adriani, M.D. (Pp. 232+xvi; illustrated. 88s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Gynecological Urology. Compiled and edited by Abdel Fattah Youssef, M.B., D.S., D.G.O., M.Ch., F.I.C.S. (Pp. 893+xvii; illustrated. £9.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Dyslipidoses. By Raul Fleischmajer, M.D. Foreword by Marion B. Sulzberger, M.D. (Pp. 509+xvi; illustrated. £6 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Procurement and Materials Management for Hospitals. By Rex H. Gregor and Harold C. Mickey, B.B.A., F.A.C.H.A. (Pp. 159+xii; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Index of Equipment for the Disabled. In Four Volumes. (Illustrated. £6.) London: National Fund for Research into Poliomyelitis and other Crippling Diseases. 1960.

Current Problems in Phoniatrics and Logopedics. Volume I. Edited by Felix Trojan. (Pp. 226+xviii; illustrated. Sw. fr. 38.) Basle, New York: S. Karger. 1960.

The Metabolism of Cardiac Glycosides. A Review of the Absorption, Metabolism and Excretion of Clinically Important Cardiac Glycosides. By S. E. Wright, Ph.D., M.Sc., A.R.I.C. (Pp. 86+viii; illustrated. 38s.) Oxford: Blackwell Scientific Publications. 1960.

The Chemistry of Lipids in Health and Disease. By H. K. King, M.A., Ph.D., F.R.I.C. (Pp. 104+vii; illustrated. 30s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Tonsils and Adenoids in Childhood. By Donald F. Proctor, M.D. (Pp. 70+xi; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Wirbelgelenk und Bandscheibe. Ihre Beziehung zum Vertebragenen Schmerz Zugleich eine Stellungnahme zur Chiropraktik und Begutachtung. By Professor Dr. L. Zukschwerdt, Dr. E. Emminger, Dr. F. Biedermann, and Dr. H. Zettel. Second edition. (Pp. 319; illustrated.) Stuttgart: Hippokrates-Verlag. 1960.

La Goutte. By S. de Sèze and A. Rickewaert, with the assistance of J. Levernieux and R. Marteau. (Pp. 268; illustrated. N.F. 47.) Paris: L'Expansion Scientifique Française. 1960.

Enzymes in Clinical Medicine. By Irving Innerfield, M.D. (Pp. 334+ix; illustrated. 89s.) New York, Toronto, London: Blakiston Division, McGraw-Hill Book Company, Inc. 1960.

Metal-Binding in Medicine. Proceedings of a Symposium Sponsored by Hehnemann Medical College and Hospital, Philadelphia. Editor Marvin J. Seven, M.D., Associate Editor L. Audrey Johnson, M.D. (Pp. 400+xiii; illustrated. £5 10s.) London: Pitman Medical Publishing Co. Ltd.; Philadelphia and Montreal: J. B. Lippincott. 1960.

Human Growth. Symposia of the Society for the Study of Human Biology. Volume III. Edited by J. M. Tanner. (Pp. 120; illustrated. 30s.) Oxford, London, New York, Paris: Symposium Publications Division, Pergamon Press. 1960.

Clinical Orthopaedics. Anthony F. DePalma, Editor-in-Chief. Number 16. (Pp. 315+xi; illustrated. 60s.) London: Pitman Medical Publishing Co. Ltd.; Philadelphia and Montreal: J. B. Lippincott Company. 1960.

The Bargainers. A Survey of Modern Trade Unionism. By George Cyriax and Robert Oakeshott. (Pp. 228; 21s.) London: Faber and Faber. 1960.

Helping the Elderly to Live at Home. By Dr. Kenneth Hazell, M.R.C.P., M.R.C.P.Ed., D.P.M. Foreword by Sir Allan Daley, M.D., LL.D., F.R.C.P. (Pp. 39. 2s.) London: The Central Council for Health Education, Tavistock House North, Tavistock Square, W.C.1. 1960.

Law for the Rich. A Plea for the Reform of the Abortion Law. By Alice Jenkins. Introduction by Glanville Williams, LL.D., F.B.A. (Pp. 95. 15s.) London: Victor Gollancz. 1960.

Laboratory Handbook of Toxic Agents. Editor-in-Chief C. H. Gray, D.Sc., M.D., F.R.C.P., A.R.C.S., F.R.I.C. (Pp. 170+viii; 20s.) London: The Royal Institute of Chemistry. 1960.

Miscellaneous Notes (Eighth Series). By F. Parkes Weber, M.D., F.R.C.P., F.S.A. (Pp. 12. 3s.) London: H. K. Lewis and Company Ltd. 1960.

Eat Well and Stay Well. By Ancel and Margaret Keys. Foreword by Paul Dudley White, M.D. Special British Edition adapted by Magnus Pyke. (Pp. 348. 15s.) London: Hodder and Stoughton. 1960.

General Anaesthesia for Dentistry. By James McNaught Inglis, M.B., Ch.B., F.F.A. R.C.S.(Eng.), D.A., and Victor Campkin, M.B., B.S., F.F.A. R.C.S.(Eng.), D.A. (Pp. 88+viii. 10s. 6d.) London: Edward Arnold (Publishers) Ltd. 1960.

Levels of Knowing and Existence. Studies in General Semantics. By Harry L. Weinberg. (Pp. 274+x. 21s.) London: Hodder and Stoughton Ltd. 1960.

Animal Drawing. Anatomy and Action for Artists. (Animal Anatomy and Psychology for Artists and Laymen.) By Charles R. Knight. (Pp. 149+vii; illustrated. $2.) New York: Dover Publications, Inc. 1960.

An Outline of Chemical Genetics. By Bernard S. Strauss, Ph.D. (Pp. 188+ix. 35s.) Philadelphia and London: W. B. Saunders Co. 1960.

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AETIOLOGY OF SARCOIDOSIS

The suggested causes of sarcoidosis are exceedingly diverse. They include infection by an at present unidentified agent, or with *Mycobacterium tuberculosis*, leprosy, syphilis, fungi, protozoa, and helminths, or tissue reaction to beryllium, silica, and pine pollen, or an inflammatory response of the type occurring in the collagen diseases. No definite proof has been provided for any of these hypotheses and the aetiology of sarcoidosis remains baffling. Particularly timely and important therefore is evidence of the causal role of *M. tuberculosis* in sarcoidosis, which Dr. J. G. Scadding has described in his Mitchell Lecture, published in the opening pages of the *Journal* this week.

Discussion of the aetiology of sarcoidosis has been confused by difficulties imposed by the definition of the disease. Dr. Scadding adopts the helpful concept that sarcoidosis is a syndrome whose principal defining feature is essentially histological and has suggested the following definition: "Sarcoidosis is a disease characterized by the presence in all the affected organs of epithelioid cell tubercles without caseation, the older lesions tending to become converted into hyalinized fibrous tissue." This makes no mention of aetiology and so allows the addition of a term indicative of aetiology to the word "sarcoidosis" if in a case which conforms to the descriptive definition of sarcoidosis there is sufficient evidence of this aetiology—for instance, "tuberculous sarcoidosis" or "beryllium sarcoidosis."

Among Dr. Scadding's series of 230 cases of sarcoidosis tubercle bacilli were isolated from 29, or 13%. In 18 cases (8%) tubercle bacilli were found without the clinical course, tuberculin sensitivity, response to treatment, or prognosis deviating in any way from that observed in the rest of the series in which tubercle bacilli had not been found, and without the appearance of any other evidence of caseating tuberculosis. The tubercle bacilli were found at all stages of the disease and at various periods from the apparent onset. In all of five cases in which the tubercle bacilli were appropriately examined they were found to be of human strain and of normal virulence for guinea-pigs. In another five cases tubercle bacilli were first found at a time of change from the clinical picture of sarcoidosis to one of caseating tuberculosis. All these cases were tuberculin-negative in the "sarcoid phase" and became tuberculin-positive when tubercle bacilli were found, and in three cases some of the clinical features of sarcoidosis resolved at this time. In another six cases tubercle bacilli were isolated at varying periods before the appearance of manifestations of sarcoidosis at a stage when the clinical picture was that of overt caseating tuberculosis.

Dr. Scadding contends that the entire illness was attributable to the tubercle bacilli both in the patients in whom tubercle bacilli were found in the "sarcoid phase" and in those in whom there was evidence of caseating tuberculosis before or after the "sarcoid phase." He suggests that the reason for the development of sarcoidosis rather than caseating tuberculosis rests on a peculiarity of the tissue reactivity of the patient. In those patients in whom a change from a caseating to a sarcoid phase or vice versa was observed, this peculiar tissue reactivity must be supposed to have developed or disappeared during the observed course of the disease.

There is good evidence for the peculiar tissue reactivity invoked by Dr. Scadding. Study of immunological reactions in sarcoidosis has revealed an abnormality characterized by poverty of reactions of the delayed hypersensitivity (tuberculin) type, while responses of the immediate hypersensitivity type remain normal or are increased.[1–3] Using the tuberculin tests as an indication of the changed immunological reactivity, Dr. Scadding and his colleagues have produced evidence suggesting that the immunological abnormality is not produced by sarcoidosis but is likely to have preceded the occurrence of sarcoidosis.[4] This immunological abnormality may have been the reason why sarcoidosis rather than caseating tuberculosis was associated with tuberculous infection. Thus the cause of sarcoidosis may have to be sought as much in the altered reactivity of the host as in external causative agents.

Attempts to grow *M. tuberculosis* from sarcoidosis tissue have generally been a notable failure.[5]

[1] Sones, M., and Israel, H. L., *Ann. intern. Med.*, 1954, **40**, 260.
[2] Citron, K. M., *Tubercle (Lond.)*, 1957, **38**, 33.
[3] Sands, J. H., Palmer, P. P., Mayock, R. L., and Creger, W. P., *Amer. J. Med.*, 1955, **19**, 401.
[4] Citron, K. M., and Scadding, J. G., *Quart. J. Med.*, 1957, **26**, 277.
[5] Longcope, W. T., and Freiman, D. G., *Medicine (Baltimore)*, 1952, **31**, 1.
[6] Nethercott, S. E. and Strawbridge, W. G., *Lancet*, 1956, **2**, 1132.
[7] Warfvinge, L. E., *Acta med. scand.*, 1943, **114**, 259.
[8] Rostenberg, A., Jr., Szymanski, F. J., Brebis, G. J., Haeberlin, J. B., Jr., and Senear, F. E., *Arch. Derm. Syph.*, 1953, **67**, 306.
[9] Michael, M., Jr., Cole, R. M., Beeson, P. B., and Olson, B. J., *Amer. Rev. Tuberc.*, 1950, **62**, 403.
[10] Gentry, J. T., Nitowsky, H. M., and Michael, M., Jr., *J. clin. Invest.*, 1955, **34**, 1839.
[11] Cummings, M. M., Dunner, E., Schmidt, R. H., Jr., and Barnwell, J. B., *Postgrad. Med.*, 1956, **19**, 437.
[12] —— and Hudgins, P. C., *Amer. J. med. Sci.*, 1958, **236**, 311.
[13] Hardy, H. L., *Amer. Rev. Tuberc.*, 1956, **74**, 885.

However, S. E. Nethercott and W. G. Strawbridge[6] claim to have found in sarcoidosis lesions diaminopimelic acid and mycolic acid, which occur in myocobacteria but not in other micro-organisms or in normal human tissue. Moreover, tubercle bacilli alive or dead, B.C.G., and lipopolysaccharide of mycobacteria may produce sarcoidosis lesions when injected into patients with sarcoidosis.[7 8]

A new approach to the problem of aetiology has been made in the U.S.A., where extensive epidemiological studies have revealed an apparent correlation between the birth-places of sarcoidosis patients and the distribution of forests.[9–11] This led M. M. Cummings and P. C. Hudgins[12] to investigate various forest products. They found that pine pollen (of two species) takes up acid-fast Ziehl–Neelsen stain like tubercle bacilli. The pollen contains diaminopimelic acid, which as already mentioned occurs in mycobacteria and also in sarcoidosis tissue. Pine pollen and phospholipid derived from it when injected into guinea-pigs produced localized sarcoid-like lesions. This is proof that substances other than mycobacteria can stimulate sarcoid-like lesions. Similar naturally occurring substances may await discovery. Epidemiological and tissue assay studies have confirmed that a disease closely resembling sarcoidosis clinically and identical with it histologically occurs in some people after the inhalation of certain compounds of beryllium.[13]

Many investigators deny that sarcoidosis is a syndrome with many causes and hold that it is a single disease due to a single unknown cause. In support of this view they point out that sarcoidosis as described round the world presents a pattern which is remarkably uniform clinically, radiologically, and histologically. However, the same might be said of erythema nodosum, a condition known to have several causes. It is probable that the causes of sarcoidosis are multiple, and vary from one part of the world to another. In Great Britain *M. tuberculosis* is likely to be one of the most frequent causes.

CONTROL OF URINARY INFECTION IN UROLOGY AND GYNAECOLOGY

The introduction of infection by catheterization is a well-known risk and constantly warned against in the textbooks. Nevertheless, the procedure is so commonly employed, and so often delegated to the inexperienced, that the appropriate precautions are occasionally apt to be overlooked. Laboratory studies in fact show a high incidence of bacteriuria after instrumentation, and, whereas clinical evidence of infection may be less evident, there can be no doubt that in some instances permanent harm has resulted. Complications are particularly likely when renal function is already impaired or when catheterization is associated with local surgical procedures, especially if it has to be repeated at intervals or the instrument is left indwelling. There seem to be two schools of thought on these problems. On the one hand. the "idealists" seek to eliminate infection altogether by scrupulous attention to all aspects of catheterization and drainage, using special apparatus and a highly trained and intelligent team of assistants and nursing staff. On the other hand are those who appear resigned to the possibility of infection following in some cases, regarding the consequences as insignificant provided free drainage is maintained. This somewhat complacent attitude may be to some extent fostered by a reliance on antibiotic therapy if infection does occur. The rational attitude no doubt lies somewhere between these two extremes, but there is little question that some improvement in the general standard of pre- and post-operative catheterization in urological and gynaecological surgery is badly needed.

Recent studies of this subject have been made by W. A. Gillespie and colleagues[1] at Bristol, and as a result a number of modifications have been suggested in the management of catheter drainage which, when adopted in combination, have been shown to reduce post-operative urinary infection. In brief, an infection rate of 83% after prostatectomy and 73% after simple emergency bladder drainage for acute retention of urine before the introduction of such measures was reduced subsequently to 6% and 10% respectively. Bacteriological investigations showed that infection of the urinary tract after instrumentation might come, from a number of sources, predominantly from other patients or from the patient's own body. The main route of infection was undoubtedly urethral, organisms either being carried up by the passage of the instrument or being conveyed by air bubbles from an open drainage bottle. As a result, a series of technical modifications were individually adopted in different order in two hospitals and the effect on the reduction of the infection rate duly noted. First, these included an attempt to sterilize the urethra by the instillation of chlorhexidine, and later a combination of chlorhexidine and mercury oxycyanide, before the passage of instruments. Secondly, attention was directed to the disinfection of catheters and cystoscopes (a procedure often inadequately and casually attended to). Drainage of catheters into an open-mouthed bottle

[1] Gillespie, W. A., Linton, K. B., Miller, A., and Slade, N., *J. clin. Path.*, 1960, 13, 187.
[9] Clarke, S. H. C., *Brit. med J.*, 1960, 2, 1491.

was abolished and a system of underwater closed drainage into a sterile receptacle introduced. Finally, a method of closed irrigation was adopted whereby free drainage could be maintained without disconnexion of the apparatus.

Although the effects of these various measures differed in degree in the two units where they were introduced, in combination they resulted in a significant decrease in urinary infection, as the figures showed. This would appear to be a notable advance in the management of cases requiring catheterization and one which should arouse interest and promote a certain amount of reflection in other centres. A similar, though somewhat less striking, reduction of infection in gynaecological cases requiring catheterization was also obtained by these measures, and it seems clear that the implications of the technique are by no means limited to urological surgery. Moreover, Gillespie and colleagues suggest that in order to avoid entirely the risk of introducing organisms pathologists should usually forgo their demand for catheter specimens from female cases and adjust themselves to report on suitably obtained mid-stream specimens as in the male. In an article published recently in this journal Mr. S. H. C. Clarke[2] submits evidence to show that mid-stream specimens of urine obtained from women give satisfactory results on culture.

There can be no doubt that infection introduced by catheterization may sometimes prove to be serious, and the report from Bristol emphasizes that before the present precautions were adopted major complications, particularly septicaemia, were caused more frequently by urological infection than by the staphylococcal infection of wounds. It is probable also that some cases of chronic pyelonephritis and others with recurrent symptoms from urinary infection may likewise owe their origin to a similar cause. The maintenance of a rigid standard of asepsis and the introduction of suitable preventive measures should thus receive the same attention as has been directed towards the broader problem of hospital cross-infection in general.

BREAD AND FLOUR

A report by the Food Standards Committee, jointly announced by the Ministry of Agriculture, Fisheries and Food, the Ministry of Health, the Department of Health for Scotland, and the Home Office, makes recommendations for legal control over the composition, description, labelling, and advertising of bread and flour.[1] The report from the main committee is supplemented by others from four separate subcommittees on questions of nutrition, analysis, flour improvers, and milk bread. The report on milk bread has already been issued in duplicated form, and been reviewed in these columns.[2]

The problems faced by the various committees have been formidable, and their decisions are obviously the fruit of careful and detailed discussion of many difficult points. In their recommendations two main motives may be recognized. Firstly, the consumer must be supplied with wholesome nutritious bread and flour. Secondly, he must be protected from being "fobbed off" with products which are incorrectly described or to which some imaginary health-giving property is attributed. His brown loaf must be made from brown flour, and not from flour coloured artificially. A suggestion that a loaf provides more than the usual amount of energy, for example, will not be allowed. To clear the way for legislation designed to protect the health and pocket of the consumer, satisfactory analytical methods must be available and equitable methods for their application worked out.

One of the questions considered was the desirability of raising the amounts of vitamin B_1, nicotinic acid, and iron at present added to flour, and whether fortification should also include pyridoxine. The 1945 Conference on the post-war loaf[3] recommended that, apart from the question of fortification with calcium, the flour used for making bread should contain stipulated amounts of three "token nutrients" (0.24 mg. of vitamin B_1, 1.60 mg. of nicotinic acid, and 1.65 mg. of iron per 100 g.). It was intended that these token nutrients would be present naturally in the flour, and that their concentration would be kept up to the required level by keeping to an extraction rate of about 80%. Thus out of every 100 parts of wheat milled only 20 parts of the coarser fractions, rich in token nutrients, were to be rejected. It was expected that the token nutrients would be accompanied by correspondingly high concentrations of pyridoxine and other lesser-known nutrients in flour. But in 1956 a Government Panel departed from the spirit of the 1945 recommendations and made the term "token nutrients" meaningless. Thus it was decided that flour could be milled at any extraction rate, provided that vitamin B_1, nicotinic acid, and iron were present at the levels previously

[1] *Food Standards Committee Report on Bread and Flour*, Ministry of Agriculture, Fisheries and Food, 1960, H.M.S.O. (4s. 6d. net.)
[2] *Brit. med. J.*, 1959, 2, 1243.
[3] *Conference on the Post-war Loaf*, Cmd. 6701, 1945, H.M.S.O.
[4] *Report of Panel on Composition and Nutritive Value of Flour*, Ministry of Agriculture, Fisheries and Food, 1956, H.M.S.O.
[5] *Annual Report on Domestic Food Consumption and Expenditure*, National Food Survey Committee, Ministry of Agriculture, Fisheries and Food, 1957, H.M.S.O.
[6] *Report of the Committee on Nutrition*, British Medical Association, 1950.
[7] *Report of the Joint Subcommittee on Welfare Foods*, Central and Scottish Health Services Councils Standing Medical Advisory Committees, H.M.S.O., 1957.
[8] Mellanby, E., *Brit. med. J.*, 1947, 2, 288.

in force. By the artificial addition of the three substances to flour, therefore, the millers could fortify flour of 70% extraction rate, or even lower, so that it could satisfy the regulations. Greater whiteness was obtained at the expense of lowering the concentration of pyridoxine and the less-well-known nutrients.

In reviewing evidence for and against the policy of fortification the Joint Nutrition Panel, whose report is included in the present publication, sought expert advice on whether any signs of disease can be seen in our population which correspond to deficiencies either of the three "tokens" or of any other nutrients which are known to be present in flour. They also perused public health records and the reports of the National Food Survey.[5] Only a few vague hints of possible nutritional deficiency were considered worthy of mention. Thus low levels of haemoglobin have been found in mothers who have had more than three children. Stillbirth rates have been higher in low-income groups than in high-income groups, in which better food can presumably be purchased. Finally, the growth rates of children have been found to be somewhat higher in high-income groups than in low, and in small families than in large. The Panel decided that, though there is no clear-cut evidence of deficiencies of vitamin B_1, nicotinic acid, or iron in the population, it is desirable to assure the protection of those groups, such as large families in the lower social classes, who may be unduly vulnerable. Fortification of flour with these three nutrients should therefore be continued at its present level, but not increased. The addition of pyridoxine to flour is held to be unnecessary. The report shows that fortification provides about 10% of our total supplies of iron, 21% of our vitamin B_1, and 15% of our nicotinic acid. However, even without fortification the intakes of these nutrients in the average household would still be slightly above the allowances recommended by the British Medical Association.[6]

In deciding whether the addition of calcium carbonate to flour should be continued the Panel faced a knotty problem. Chalk was first added to flour during the second world war in order to compensate for the decalcifying action of the increased intake of phytic acid caused by the raising of the extraction rate. Now that the extraction rate has fallen back to pre-war levels the original purpose for adding the chalk has gone. Some authorities think that an unduly high intake of calcium may promote pathological calcification in arteries and joints, while others believe that calcium will merely be drawn from the bones if inadequately supplied in the diet. The Panel was influenced in deciding to keep chalk in the flour by evidence that if it is left out the amount obtained by certain vulnerable social groups would become very low. Another point to be considered was the recent recommendation by the Joint Subcommittee on Welfare Foods[7] that the amounts of vitamin D added to certain infant foods and cereals should be reduced. Since the requirements for vitamin D and calcium are to some degree interrelated, it seemed desirable to give time for any effects on public health of this decision to become apparent before further changes were made. An anomaly, fully recognized by the Panel, is that chalk is not added to wholemeal flour. Since such flour contains much more phytic acid than other types of flour its fortification with chalk would seem to be particularly desirable according to the arguments which originally prompted the addition of chalk.

The Panel was also asked to give its ruling on how much protein must be present in bread before it is described as "protein-enriched," and decided on a minimum of 21–22%. In "starch-reduced" bread the carbohydrate must be reduced to less than 50% of its normal value. No food, it was decided, can properly be described as "slimming bread," and no advertisement should be allowed to suggest that particular types of bread have a specific weight-reducing property.

The report of the Preservatives Subcommittee on Flour Improvers reviews the need for the treatment of flour with various bleaching agents, which merely increase its whiteness, and so-called maturing agents, which increase the porosity of the bread and hence the size of the loaf. Some agents combine both these properties. No strong justification could be seen for the use of bleaching agents, and it was recommended that the number permitted should be kept to a minimum, and that maximum levels should be prescribed for those permitted. Maturing agents were held to be essential if the baking of the type of bread alleged to be preferred by the public is to continue. The chemical changes which improve the baking qualities of flour are oxidative, and they occur slowly when flour is stored in the presence of air. Immense storehouses would have to be erected if all flour had to be matured in this way. Apart from the great expense there would be risks of infestation by insects and rodents, and the final product would not be uniform. Since the discovery[8] that nitrogen trichloride, once the most commonly used maturing agent, produces in flour a substance which is highly toxic, at least to dogs, most millers have relied mainly on chlorine dioxide for the rapid and efficient improvement of flour. The strong oxidizing action of chlorine dioxide, however, almost completely destroys the vitamin E which is naturally present in the flour. Apart from this, experiments on various animals have failed to reveal any toxicity or injury to the nutritive value of the flour, except possibly for reduced growth rates in multi-generation experiments with rats. In the words of the sub-

committee, "There is no evidence at present that the consumption of flour treated with chlorine dioxide, in mixed dietaries containing other sources of vitamin E, is harmful to man." It recommends that all bleaching and maturing agents should be subjected to well-designed, long-term chronic toxicity studies. Pending such studies flour to be used for making bread should be treated only with benzoyl peroxide (bleaching agent), ascorbic acid (maturing agent), potassium bromate (maturing agent), ammonium or potassium persulphate (maturing agent), or commercial chlorine dioxide (maturing agent). For cake flour only, heavy treatment with chlorine is to be allowed, and sulphur dioxide may be used for preparing flour suitable for making biscuits.

The Joint Nutrition Panel, in common with the Preservatives Subcommittee, mentions the need for further research on various points. We may hope that these hints will be acted upon by those in authority. For the present there seems some danger that the introduction of a carefully devised system for the analysis and control of flour may protect the consumer from financial victimization but do very little to benefit the state of his health.

CHANGES IN THE RETINA AFTER HAEMORRHAGE

"After vomiting blackish—sometimes bloody—matter the patient complains of headache and the eyes do not see." In these words Hippocrates[1] alluded to the visual impairment which may follow excessive blood loss. This then is a clinical observation of the greatest antiquity; yet, considering the frequency of haemorrhage, visual symptoms are relatively uncommon, and, curiously, occur almost exclusively with recurrent bleeding in chronic medical conditions rather than in surgical or traumatic cases. In the Franco-Prussian war, for instance, no visual disturbances could be attributed to surgical haemorrhage alone,[2] while C. Goulden[3] stated that of all the patients with haemorrhage he had seen in the first world war none had complained of loss of sight. It has been estimated that 70% of the cases occur after haemorrhage from the gastro-intestinal tract or from the uterus, particularly after childbirth and miscarriage, while others have occurred after blood-letting,[4] nasal bleeding,[5] urethral bleeding,[6] and in haemorrhagic diathesis.[7] On the surgical side, some of the conditions causing blindness have been prolonged bleeding from dental extraction,[8] from thyroidectomy,[9] and from pulmonary excision.[10]

The amblyopia usually develops between the third and seventh days after haemorrhage, but may be delayed for a much longer time; it may be partial or complete, transitory or—if succeeded by optic atrophy—permanent, and in most cases it is bilateral. In rare instances the ophthalmoscopic appearances have been normal,[11] but usually there is pallor of the disk, attenuation of the vessels, and neuroretinal oedema, which occasionally may be so severe as to resemble the appearance of the fundus in central arterial occlusion. Sometimes the presence of haemorrhages and cotton-wool exudates may simulate those of renal or albuminuric retinopathy.[12]

These features are well recognized in ophthalmology, but that blood loss may lead—probably more commonly—to changes in the fundus oculi without visual symptoms is less widely appreciated, partly because these changes have not been especially sought and partly because they fail to attract attention. In contemporary works on ophthalmology they have received little mention, and none in works on gastro-enterology.

In an interesting and beautifully illustrated paper M. A. Pears and Sir George Pickering[13] now report seven cases in which papilloedema, haemorrhages, and exudates appeared in the retinae after recently sustained massive gastro-intestinal haemorrhage. The fundus picture was very similar to that seen in the malignant phase of hypertension; indeed, it was this resemblance that particularly aroused the authors' interest.

Papilloedema occurs in both conditions (though more severely in hypertension), while the exudates and haemorrhages are indistinguishable in the two and may be equally evanescent in both. So close is the resemblance that the presence or absence of hypertensive vascular changes may be the only point of differentiation ophthalmoscopically, and one wonders what relationship might exist between retinopathies so alike and yet arising in conditions with no apparent kinship.

Histologically the neuroretinal oedema and the haemorrhages are identical, and in both cases the fluffy exudates are known to consist of focal oedema in the stratum opticum with necrosis and varicose degeneration of the nerve fibre layer.[14] The underlying process would seem most probably to be one of ischaemia and transudation. Yet how does this arise and why should it be so sharply localized? Pears and Pickering feel there is little evidence to support the hypothesis that anaemia alone could be the ultimate cause of the retinal lesions occurring after haemorrhage, and believe that a sudden fall in circulating blood volume is a more important factor. A raised intracranial pressure, known to occur in both conditions, could account for the papilloedema, but according to Pears and Pickering the exudates could certainly not be explained on this basis. It is possible that the common factor producing the ischaemic lesions is localized spasm of the arterioles, for such lesions have been demonstrated in hyper-

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tensive rats, in the retina by K. Abt and R. Brückner[15] and in the brain and other tissues by F. B. Byrom.[16]

We require to know much more about the reactions of the smaller retinal vessels themselves, not only in hypertension and exsanguination but also in other conditions showing similar retinal lesions such as systemic lupus erythematosus and liver disease.[17–19] The most pressing need is for further histopathological studies of the eyes in these conditions, and particularly for relevant experimental work on the retinal vessels of laboratory animals. No doubt the observations of Pears and Pickering will stimulate more work on these problems.

GENETICS AND LEUKAEMIA

The aetiology of leukaemia in man remains an intractable problem. One environmental agent which may cause leukaemia is known: radiation in large doses has been shown to cause granulocytic leukaemia, both by studies of survivors of the atomic explosions in Japan[1] and by studies of patients treated for ankylosing spondylitis.[2] The question whether diagnostic radiology of the pregnant woman plays some part was discussed in these columns last week in relation to the work of Alice Stewart and colleagues[3] and Court Brown and colleagues.[4] An environmental agent which is regarded, particularly in France, as leukaemogenic is benzene,[5] and last week in this journal R. H. D. Bean[6] raised the possibility that phenylbutazone may be another. But the known contribution of environmental agents to the aetiology of leukaemia is, as yet, small.

On the genetic side there is one clear association between abnormal constitution and leukaemia. That is the increased risk of leukaemia in mongol children.[3 7 8] However, this is no indication that genetic factors are important in leukaemia in normal children. In a few normal children the leukaemia may be attributed to a recessive gene. Three families are known in which three or more brothers and sisters have been affected by leukaemia.[9 10] These circumstances are highly selected, but cannot reasonably be attributed to chance. Familial infection is a possibility, but in two of the three families the children were the offspring of a consanguineous marriage, suggesting that in these particular patients a recessive gene was the aetiological agent. To assess the part played by genetic factors in leukaemia as a whole, large-scale twin or family studies are needed, and it is unfortunate that no large study of twins has yet been made. Several instances of leukaemia in both of monozygotic twins have been reported, but these are not part of a consecutive series, and so are of limited value. Three monozygotic co-twins of a consecutive series of patients with leukaemia reported by A. G. Steinberg[9] were all unaffected.

A number of large-scale family studies have been reported. An early study from Denmark,[11] published in 1947, indicated that there was an increased risk of leukaemia, cancer, and pernicious anaemia in the near relatives of patients with leukaemia as compared with controls. There are indications, however, that a study of the controls in this series was not complete, and further studies of the same kind have not confirmed the findings. Recently Steinberg,[9] in Massachusetts, has made a careful family study of the relatives of 249 children with actual leukaemia, and found no increase in the incidence of leukaemia or in other forms of cancer among the near relatives of the patients. When the disease is viewed as a whole, therefore, there are no indications that genetic factors play a major part in its causation. The picture at present is, then, of a small proportion of cases caused by known environmental agents, a small proportion associated with the chromosome abnormalities of mongolism, or caused by one or more recessive genes, and a great majority of cases in which the aetiology remains unknown.

CAMBRIDGE VOTE POSTPONED

The salary crisis at Cambridge—described in a leading article in last week's *Journal* (p. 1579)—was not after all brought to a head this week by a vote of the University, and controversy continues. The *Cambridge University Reporter* of November 23 contains a full account of a meeting of the Senate at which the General Board's reports on stipends were discussed. A few days after this meeting the council of the Senate decided to refer the remarks made at the discussion to the General Board and to defer the ballot until the Lent term.

VISIT OF CHINESE DOCTORS

Contacts between Russian doctors and their British colleagues have become increasingly frequent during the past few years. Opportunities of meeting medical men from the mainland of China are, however, all too rare. We therefore offer a special welcome to the six eminent Chinese physicians who, as delegates from the Chinese Medical Association, are now in Britain at the invitation of the Royal College of Physicians of London. According to their various interests they are visiting centres of research and special practice in the United Kingdom. The delegation is composed of: Dr. HSUEH KUNG-CHUO, head of the delegation, vice-president of the Chinese Academy of Medical Science; Professor CHANG SI-CHUN, deputy director of the Experimental Medical Research Institute of the Chinese Academy of Medical Science and Professor of Physiology; Dr. LAN SI-CHUN, director of the surgical department of the Shanghai Second Medical Institute; Professor CHU TI-TUNG, head of the pathological biology department of the Shanghai First Medical Institute; Professor LIANG CHIH-CHUAN, deputy director of the biochemistry department of the Chinese Academy of Medical Science; Dr. CHU SHOU-HO, deputy director of the paediatrics department of the Peking Sino-Soviet Friendship Hospital.

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VALUE OF THE SPECIALIST'S REPORT

BY

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Since the introduction of the N.H.S. Act of July, 1948, the medical profession has become increasingly aware of a lack of efficient co-ordination between the general practitioner and the specialist. The G.P. may complain that the specialist either avoids the specific problems for which his services were asked or leaves him in the dark about diagnosis or treatment planned for the patient. The specialist may reply that the G.P. is not interested in knowing more about his patients, and will quote the "please see and treat" type of letter as typical. He may even disregard the contribution the G.P. has to offer towards diagnosis and treatment, without realizing that eventually the G.P. will have to bear the responsibility for the patient's health. There is a division of responsibility for the patient's welfare between the two, and if the roles of specialist and G.P. are not clearly defined the patient suffers.

The G.P., because of his accessibility to the patient and the obvious facilities he has for long-term observation and continuity of treatment, is responsible for the overall management of the patient, who goes to the specialist on his advice, but will return once the latter has fulfilled his role. He is not a sorting clerk, and should be able to follow his patient through either directly or indirectly. He would like to compare his initial diagnosis and treatment with what has been discovered by the specialist in hospital. For this he requires an adequate report, which should reach him before the initial freshness of the clinical picture has been wiped from his mind by several weeks of full surgeries.

The specialist, on the other hand, by concentrating on one particular field, has had the opportunity to acquire the skill and knowledge to deal with certain diagnostic and therapeutic problems which, coupled with the facilities to which he has access in hospital, enable him to cope with some aspects of diagnosis and treatment which are out of the reach of the G.P.

In human relationships, negative points in a situation are the ones that tend to remain fixed in the mind and lead to resentment and misunderstanding: it was felt that an objective study of the mechanism of the situation would be helpful.

Method of Investigation

This study is an attempt to find: (*a*) factors which may enhance or detract from the specialist's contribution to the diagnosis and treatment of the patient; and (*b*) which of these factors could be modified to the benefit of the patient and of the specialist–G.P. team considered as a therapeutic unit.

In order to do this 500 cases which had been referred to specialists were selected at random from the records of a practice which cover a period of five years. Obstetric cases were excluded from the study. In all letters of referral, advice or opinion was requested from the specialist. Four points were considered important in assessing the value of the reports.

1. *Contents of the Reports.*—The reports were classified as useful or vague and useless. A report was regarded as useful if it gave clear, practical indications with regard to diagnosis or treatment. A frank indication from the specialist that he was unable to provide a diagnosis or definite line of management was also considered to be useful. If the report did not meet these basic requirements it was considered vague and useless. It should be pointed out that the diagnosis or treatment which afterwards proved to be wrong was tabulated as "useful," as the purpose of this study was to assess the value of the report itself and not diagnostic or therapeutic acumen. An independent agreement of all three members of the team was required before any report could be called "useless."

2. *What was Told to the Patient.*—The reports were also studied to see whether any mention is made of what was told to the patient about his illness, and it was felt that it is important that there should be a connexion or congruity between what the G.P. and the specialist tell the patient about "what is wrong with him."

3. *Information about Proposed Operation.*—In the case of patients who were subsequently operated upon, we noted whether the G.P. was informed or not that the operation would be performed at an approximate date.

4. *Reports Timely or Late.*—A report from the specialist arriving after the patient has come back to the surgery to inquire about the outcome of his visit to or stay in hospital loses much of its value. The time of arrival of the report was studied from different angles. (*a*) Out-patients: whether the letter arrived before or after the patient attended surgery or was visited. (*b*) In-patients: (1) Whether a letter was received after admission and, if so, whether it arrived within the first 48 hours after entering hospital. Emergencies and ordinary admissions were considered separately. (2) Letter on discharge: whether within 48 hours of discharge or after. (3) Letter arriving at surgery before or after patient.

Results

1. Contents of Reports

In only 4% of cases was the letter "vague and useless." This was far below what had been anticipated by members of the team, who, before calculating the results, had each predicted a much higher figure. This shows the effect a relatively small number of unsatisfactory reports can have. It also implies an overall high standard of specialist help being available. However, in the practice studied there are 15 hospitals within a radius of about two miles, allowing for a wide choice of specialist services. It would be interesting to compare a similar survey in a country practice where this choice is restricted.

In most of these unsatisfactory reports, when analysed individually, the following pattern was found to recur: (*a*) They repeated what the G.P. had already written in his letter of referral, without adding any conclusion or judgment. (*b*) They answered some point other than the specific problem posed in the letter of referral,

ignoring any statement made in the letter. (*c*) They quoted inconclusive laboratory and *x*-ray reports without adding an opinion.

2. What was Told to the Patient

In only 6% of cases was there any indication of what was said to the patient about his illness. It is unlikely that in the 94% of cases no information at all was given to the patient during the consultation, so we must assume that in many cases the specialist did not think it worth telling the G.P. what he had said. The G.P. may have to give some explanation about the illness, symptoms, or management to the patient. If he has no information about whether the specialist has spoken or not to the patient about this, or about the way he may have approached the subject, a contradictory impression can be created, producing unnecessary doubts and anxieties. One large London teaching hospital uses a printed discharge form which includes a heading, "Information given to patient."

3. Information Given about Proposed Operation

Fifty-one cases were operated on in connexion with conditions for which they had been referred, and in only 20 (39%) of these was the G.P. told that operation was proposed. In only one case was he actually informed just beforehand that the patient was about to undergo an operation.

4. Reports Timely or Late

OUT-PATIENTS

Out of a total of 364 out-patient referrals, 28 (8%) of the reports arrived after the patient had been back to the surgery and had had to be told by the G.P. that he was waiting for the specialist's report. Most of the reports arrived in the second week after the patient's appointment, but as in many cases the patient did not return to the surgery until several months after for some other complaint, the proportion of the patients arriving before the report is relatively small, though large enough for the delay to be felt. These patients often express surprise when told the hospital report has not arrived.

IN-PATIENTS

(*A*) *Letter Arriving Within 48 Hours of Admission.*—(1) *Emergency Admisions*:—Out of a total of 71 emergency admissions, in only 8 (11%) was a report received within the first 48 hours. This finding is regarded as important, because only through receiving a prompt report can the G.P. feel the continuity of personal care, check his provisional diagnosis while the case is still fresh in his memory, and reassure the relatives that come to the surgery or stop him on his rounds, requesting information. The habit of writing such a letter might also prove a stimulus to the hospital staff. (2) *Ordinary Admissions*:—Out of 65 ordinary admissions, in 11 (17%) the report arrived within 48 hours. These cases are not so important as emergencies, but a printed form would be helpful, especially if the patient had been referred some time previously.

(*B*) *Letter While Patient is in Hospital.*—Out of a total of 136 hospitalizations, in only 32 (23.5%) was a letter received while the patient was in hospital: in the remaining 104 admissions the G.P. had no notification of admission whatsoever.

(*C*) *Letter on Discharge.*—Out of 136 in-patients, in only 41 (30%) was a letter received within 48 hours of discharge.

(*D*) *Discharged Patient Arrived Before Hospital Letter.*—Out of 136 in-patients, 19 (14%) reached the G.P. before any communication had been received from the hospital (see Table).

Summaries.—90% of summaries arrived one or two months later.

Pathological Reports.—When pathological reports or tests were received from hospitals which offer those facilities to G.P.s 100% of the replies arrived on time.

Distribution of Cases in Which Advice was Received from Teaching and Non-teaching Hospitals Within 48 Hours of Admission or Discharge

	Teaching	Non-teaching	Total
Admission ..	12 (14%)	7 (14%)	19 (14%)
Discharge	32 (37%)	9 (18%)	41 (30%)

Conclusions and Suggestions

It was found in this practice that a high standard of specialist help is available. Several deficiencies have become obvious, and there seems to be scope for improvement.

The main factors which detract from the value of the specialist's report in the efficient functioning of the specialist–G.P. therapeutic unit are extrinsic to the report itself: they depend entirely on the arrival of the report at a time when the G.P. needs it or is in a receptive state to make the most of it.

Timely and adequate communication must be maintained between the two members of the unit, but any improvements to be acceptable should be applicable without increasing the paper-work of either specialist or G.P. or their ancillary help.

Within the framework of the present system the following suggestions would increase the value of the report and therefore the therapeutic efficiency of the specialist–G.P. unit.

1. A definite answer regarding diagnosis, treatment, or management. If, owing to the nature of the case, the specialist is not in a position to give it, there should be frank recognition of the fact.

2. If the patient has been told something about his illness or treatment, the nature of this explanation should be disclosed.

3. A timely report is necessary, especially in cases where the nature of the illness or the anxious character of the patient indicates to the specialist that an early return to the G.P. can be predicted.

4. A short report should reach the G.P. within 48 hours of an emergency admission.

We concluded that the value of the specialist's report largely depended upon effective communication being established between him and the G.P.

Bournemouth probably has more registered nursing-homes than any other area in Great Britain, and, says the *Annual Report of the Medical Officer of Health 1959* for the County Borough of Bournemouth, it is extraordinarily difficult to maintain a universally high standard, particularly as the powers of the local authority's inspecting officers are limited to the building, its equipment, and its staff; far too often the standard of these homes has deteriorated. It is difficult to cancel a registration once it has been given, and it is felt that the law should require annual registration, and that more precise standards of staffing should be laid down by the Ministry of Health.

STANDARDIZED QUESTIONARIES ON RESPIRATORY SYMPTOMS*

In recent years various groups of investigators have studied the epidemiology of chronic respiratory disease both in industry and in the general population in Great Britain. In most of these surveys questionaries, completed by interviewers, have been used to establish the prevalence of common respiratory symptoms, in particular those associated with chronic bronchitis.

These symptoms vary greatly in severity—for example, from an occasional dry cough to a profuse productive cough persisting throughout the year. If the results of surveys in different populations are to be compared (and such comparisons are important aetiologically), certain levels or grades of severity of symptoms must be defined, and the questions standardized so that the same subjects are likely to be classified in the same way by independent observers. Considerable bias in estimates of the prevalence of symptoms may arise without such standardization (Cochrane *et al.*, 1951; Fletcher and Oldham, 1959). In recent years a more or less standard questionary has been adopted by most investigators in this field, and it has been shown (Fairbairn *et al.*, 1959; Higgins *et al.*, 1959) that, with appropriate care, systematic errors in diagnosis may be kept small.

In the summer of 1959 a subcommittee† of the Medical Research Council's Committee on the Aetiology of Chronic Bronchitis, all of whose members had had considerable experience in the use of respiratory questionaries in field work, met to formulate a standard questionary for future use in such studies. Two questionaries have been agreed upon: a short one with only those questions which are essential in order to estimate the prevalence of chronic bronchitis; and a longer one with a number of other questions of less certain value. Both questionaries contain questions on smoking, for this habit has such a profound effect on the prevalence of bronchitis that standardization for its influence is essential. The short questionary provides for a brief occupational history, the longer one for a full occupational and residential history. Space is provided in both questionaries for further questions which may be required in special circumstances, for recording sputum volume, for the results of ventilatory function tests, and for other clinical and radiological findings. Instructions for the use of the questionaries and suggestions for coding the replies have also been agreed upon.

The short questionary seldom takes more than five minutes to complete. The long one usually takes 10 minutes, and the full residential and occupational history, according to its complexity, takes another 5 to 15 minutes.

These questionaries and instructions have been printed and made available with the agreement of the Medical Research Council's Committee on the Aetiology of Chronic Bronchitis, and copies may be obtained from Dr. C. M. Fletcher, Department of Medicine, Postgraduate Medical School, Ducane Road, London W.12.

*A statement prepared for, and approved by, the Medical Research Council's Committee on the Aetiology of Chronic Bronchitis.

†Dr. C. M. Fletcher (chairman), Dr. M. Clifton, Dr. A. S. Fairbairn, Dr. J. Fry, Dr. J. C. Gilson, Dr. I. T. T. Higgins, Professor A. Mair, Professor J. Pemberton, Dr. J. M. Rogan, Dr. D. H. Smith, and Dr. C. H. Wood (secretary).

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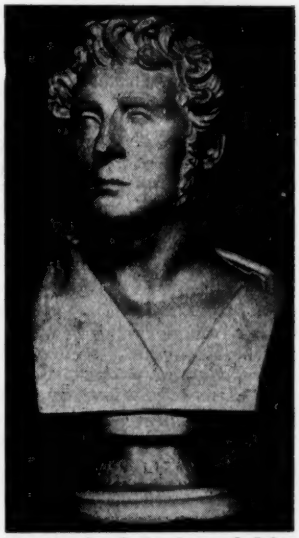
Nova et Vetera

JOHN LIZARS

CENTENARY OF A FORGOTTEN PIONEER OF THE SURGERY OF TRIGEMINAL NEURALGIA*

To his contemporaries Lizars was not a whit less in stature than any one of the brilliant company of surgeons of Edinburgh of his time, yet posterity has never conferred upon him the ageless esteem which Liston and James Syme have received. Among Lizars's numerous contributions to surgery, the account he gave of the first neurotomy of one of the deeper branches of the trigeminus for the relief of neuralgia is of particular interest to the neurologist.

In a well-documented paper published in the *Edinburgh Medical and Surgical Journal* in 1821[1] he describes a patient with trigeminal neuralgia which he relieved in December, 1819, by dividing the mental nerve at the point of its emergence from the mental foramen. The patient remained free from symptoms for twelve months, after which the "same torturing pains returned." As the patient had "no faith in anything but the knife," Lizars again divided the nerve at the mental foramen. However, neither this operation nor cautery, which was applied later, relieved the pain. The patient was prevailed upon to allow the application of moxa, which was equally ineffective. Accordingly on March 15, 1821, Lizars, after making a perpendicular incision inside the mouth close to the coronoid process, introduced a gum lancet between the bone and internal pterygoid muscle. "When the lancet reached the seat of the inferior maxillary nerve, the pain he experienced was intolerable; and it was with difficulty he could sit till I cut the nerve completely. From this moment there was a sudden satisfactory termination to all his suffering." Writing in August, 1821, Lizars says, "The other day I saw him toiling in the field with apparently great enjoyment of life."



Photograph of the bust of John Lizars in the Royal College of Surgeons, Edinburgh.

John Lizars was born in 1787 and was the son of Daniel Lizars, an artist in Edinburgh "considered to be very eminent in his profession." On leaving the High School he

*An abridged communication made to the Osler Club, London.

was articled as a pupil to John Bell for five years. In 1809 he obtained his diploma from the Royal College of Surgeons in Edinburgh and in the same year sailed to the Mediterranean as an assistant surgeon in the Royal Navy, "where he saw extensive practice, especially in the treatment of gun-shot wounds." At the conclusion of the war in 1815, he returned to Edinburgh. In 1821 after a warm contest he was elected professor of surgery to the Royal College of Surgeons by a considerable majority of the votes of the Fellows.

For many years the University and College vied with each other to secure the greater share of the annual enrolment of medical students. This rivalry became all the keener when during the decade 1830 to 1840 the number of medical students in Edinburgh—probably because of the ascendancy of the medical schools in London—dropped by one-half. The clash of interests between these two institutions contributed in no small measure to the celebrated lawsuit in which the parties concerned were the professors of surgery of the University and College respectively.[2] In his *System of Surgery* Lizars enjoined that in every operation about the anus particular care should be taken to avert post-operative haemorrhage. For this reason he advocated the insertion of dry lint into the gut. He then went on to say: "Nor is it improper as an additional warning here to mention a case which was under the care of our professor of clinical surgery a few years ago. He operated on a gentleman for a slight fistula in ano, left the part inadequately defended, and dreadful haemorrhage ensued." Syme, who was the professor of clinical surgery referred to, at once imputed malicious intentions to this remark and sought legal redress by a claim for £1,000 damages and a further sum of £100 costs.

Lizars's defence was that he had "not indulged in animadversion" and that "he merely cited the case to illustrate the importance of practical advice." During the hearing his counsel claimed that the whole of the University, professors as well as students, was divided into two great parties, "the Pluggites and Anti-Pluggites," and then endeavoured to persuade the jury that the case was "one of those paltry quarrels a great deal too characteristic of the medical profession, and ought to be treated as undeserving the attention of the Court." The jury, however, after an absence of ten minutes awarded £50 damages to Syme, and the offending passage had to be expunged from the book.

When Lizars's tenure of professorial office terminated shortly after this trial, Syme succeeded in dissuading the College from re-electing him, and the opportunity was taken to abolish the chair altogether. In the following year Lizars was an unsuccessful candidate for the University chair when this was rendered vacant by the death of Sir Charles Bell, the younger brother of John Bell. Thus deprived of all active association with the College and Infirmary, Lizars's private practice declined, and his sudden death on May 21, 1860, was not without suspicion of being due to laudanum.

Barely a year had elapsed since the death of John Bell, his teacher and partner, when Lizars's paper on neuralgia was published. John Bell, in his *Principles of Surgery*, claimed that he had "constantly endeavoured to moderate the rage for operations, and to inspire a just and rational reliance on the provisions of nature for the cure of diseases." Lizars heads his paper by a short citation from this book, but, by taking the quotation out of its context, he succeeds in conveying a diametrically opposite view. "Operations have come at last to represent the whole science" is what Lizars quotes, and believes, omitting to complete the passage, which continues as follows: "and the surgeon, far from being valued according to his sense, abilities, and general knowledge, is esteemed excellent only in proportion as he operates with skill." To leave the reader in no doubt as to his own standpoint, Lizars opens his paper as follows:

(*Continued at foot of next column*)

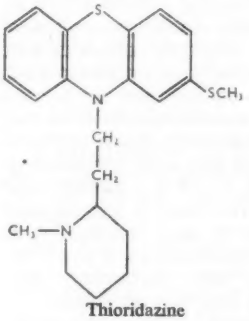
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

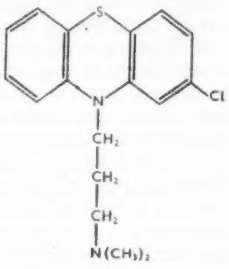
Thioridazine

"Melleril" (Sandoz).

Chemistry.—Thioridazine is a phenothiazine derivative, with the relationship to chlorpromazine shown by the following formulae:



Thioridazine



Chlorpromazine

Pharmacology.—This drug has anticholinergic and adrenergic-blocking actions. It has little anti-emetic or hypothermic action, but is otherwise comparable in its effects to chlorpromazine.

Therapy.—Like other phenothiazines, the main use for thioridazine is in the treatment of patients with schizophrenia. It is also of value in the treatment of mania, and in controlling the agitation that may occur in depressive states. Dosage is similar to that of chlorpromazine, and up to 600 mg. a day, or more, may need to be given in acute psychoses.

Side-effects.—These are similar to those of other phenothiazines. Extrapyramidal complications are said to be less of a problem, but drowsiness, dryness of mouth, dizziness, and faintness are not uncommon.

N.H.S. Basic Price.—10-mg. tabs., 100 for 6s.; 25-mg. tabs., 100 for 10s.; 50-mg. tabs., 100 for 19s.; 100-mg. tabs., 100 for 36s.

(*Continued from previous column*)

"This case I am induced to communicate as it resisted all remedies employed but the knife." As to Lizars's skill and the masterly audacity with which he wielded the knife, there cannot be any doubt. After describing the operation which he had originated for the excision of the upper jaw he says: "So little does this operation disfigure the countenance that a surgeon who saw one of my patients inquired whether it was the upper or lower maxillary bone that I had removed." In the days long before antiseptics and anaesthetics he was the first in Britain to perform ovariotomy, to ligate the innominate artery for aneurysm, and to remove the lower jaw. His boldness as a surgeon is revealed by such prophetic proposals as "to puncture the brain in acute hydrocephalus, and to treat prostate by cutting out the entire gland"—proposals which Syme quoted with derision.

SIMON BEHRMAN.

REFERENCES

[1] Lizars, J., *Edinb. med. surg. J.*, 1821, vol. 17, p. 529.
[2] Macgregor, S., *Full Report of the Jury Cause, Syme v. Lizars*, 1840. Edinburgh Printing and Publishing Co.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Health of Executives

SIR,—Nobody is going to deny the importance of early diagnosis in coronary disease. However, as an industrial medical adviser who has to deal with a large number of top executives, I am all against these princes of industry attending conferences on purely medical topics. True, they live under constant and considerable strain, but the commonest cause of pain round the heart is still indigestion, and to put thoughts of heart disease into their minds must inevitably create a commercial aristocracy of cardiac neurotics.

Such conferences should, in my opinion, be solely for members of the medical and nursing professions, who should do everything in their power to encourage executives to have regular medical examinations.—I am, etc.,

Cow and Gate Ltd.,
Guildford. DICK GLOVER.

Barrier Creams

SIR,—As an industrial medical officer I am in firm agreement with the point of view expressed by Dr. F. Ray Bettley in the Malcolm Morris lecture on "Some Dermatological Hazards of To-day" (November 19, p. 1467) that, in relation to barrier creams, "we cannot recommend the use of an application whose exact composition is not made known to us."

For this reason, in the system of preventing occupational dermatitis for which I have been responsible for the past 20 years in the Rolls-Royce Scottish group of factories and in those of other companies whom I advise in these matters, no use is made of proprietary barrier creams. This approach was emphasized in a paper[1] on "The Preventive Aspects of Dermatitis and Allied Disorders" which I read before the Section of Dermatology at the Annual Representative Meeting in Glasgow in 1954. Also, this viewpoint was an important part of my evidence in a recent test case[2] when my system was challenged for not providing a certain proprietary barrier cream to prevent cutting-oil dermatitis. In the Court of Session in Edinburgh, and later in the House of Lords, the verdict was in my favour.—I am, etc.,

Rolls-Royce Ltd.,
Glasgow S.W.2. EDWARD COLLIER.

REFERENCES

[1] *Transactions of the Association of Industrial Medical Officers*, 1955, 4, 120.
[2] *The Scots Law Times*, January 16, 1960, p. 9.

SIR,—Dr. F. Ray Bettley's authoritative remarks (November 19, p. 1467) on the value of barrier creams are welcome. They will be read with interest by medical officers in industry. Some already hold the opinions he has stated, others will be grateful for the guidance he has given, a few may see in them a challenge.

During the first world war, Dr. Benjamin Moore introduced a modification of the B.P. water-soluble casein varnish with the object of reducing skin absorption in T.N.T. workers.[1] This was perhaps the first large-scale use of a barrier substance, and the value of this measure was shown by urinary excretion tests. It was but a short step to assume that the same substance would reduce skin irritation, and, although no real evidence was produced to show that this assumption was correct, it somehow came to be accepted.

In the second world war, barrier creams were introduced into many types of industry with the hope that they might reduce industrial dermatitis. Various bases were tried, and colouring, preserving, odorous, and antiseptic agents were added to make them cosmetically attractive and further the claims of their makers. Their manufacture had by now become a business proposition, workers were putting them to a variety of cosmetic uses at home as well as at work and trying them out as remedies for various skin lesions. Primary irritation following the use of these creams was not uncommon, and sensitization—usually traced to one of the added agents—occurred from time to time.

It may seem curious that after such long and intensive experience in the use of barrier creams no scientific evidence has been produced to show their practical value. This can be explained by the fact that it is difficult to design a properly controlled experiment that will satisfy statistical criteria, and even more difficult to apply such an experiment to industry. To summarize the facts: (1) Barrier creams can cause primary irritation and sensitization. (2) If incorrectly used they can enhance the harmful effects of industrial irritants (and increase absorption). (3) There is no practical evidence to show that their influence on the incidence of industrial dermatitis is significant.—I am, etc.,

Royal Aircraft Establishment,
Farnborough, Hampshire. A. L. LEIGH SILVER.

REFERENCE

[1] Moore, Benjamin, *Medical Research Committee, Special Report No. 11*, 1917. H.M.S.O., London.

Penicillin Urticaria

SIR,—I would like to congratulate Dr. F. Ray Bettley on his stimulating Malcolm Morris Lecture (November 19, p. 1467) and comment on one of the problems he raises.

Urticaria initiated by penicillin but persisting long after the injections have been stopped is a not uncommon occurrence nowadays, but I wonder if this is a reaction specifically due to penicillin. During the war the commonest cause of transient urticaria was the prophylactic injection of T.A.B. and other sera. In almost all these soldiers the weals disappeared quickly, but in a few they persisted for months. I believe that at least some of the patients referred to by Dr. Bettley are showing a similar non-specific reaction, only that penicillin is now the commonest cause of urticaria. This view coincides partly with Dr. Bettley's fourth suggestion that "the action of penicillin has been to induce the condition of ordinary chronic urticaria in which an allergen cannot be convincingly identified." The impression one gets in these patients is that following an attack of urticaria, which may well initially have been a true antigen–antibody reaction, their skin becomes unstable and some chemical reaction is facilitated so that it now occurs spontaneously or under the influence of some stimulus other than the original one. Some people may be predisposed to such an event and only require an attack of acute urticaria of whatever origin to set it going.

Dr. Bettley's truly judicial summing-up of the barrier-cream problem will appeal strongly to all those who are reporting on patients with industrial dermatitis claims against employers whose only negligence has been their failure to provide a barrier cream. Nevertheless, despite lack of statistical evidence, I find barrier creams useful when I am doing dirty work in the garden.—I am, etc.,

Leeds 2. F. F. HELLIER.

"Celbenin"-resistant Staphylococci

SIR,—We would like to emphasize the caution which should be exercised in the evaluation of the new synthetic penicillins—namely, the last and more potent one: sodium 6 (2,6 dimethoxybenzamide) penicillanate monohydrate (BRL 1241; "celbenin," "staphcillin"). We had the chance to evaluate the drug ("staphcillin" supplied by Bristol Laboratories Inc., U.S.A.) in our research laboratory. Our results are going to appear soon. Although we did not find any staphylococcus strain originally resistant to the new penicillin (120 strains tested by serial dilutions), our findings thus far agree with Dr. Mary Barber's (September 24, p. 939) that resistance is rather easily acquired by staphylococcus *in vitro*. Out of 20 coagulase-positive, penicillinase-producing *Staphylococcus aureus* strains, all resistant to penicillin G, none of which grew in a concentration of 0.3 μg./ml. of BRL 1241, all have acquired within 20 days a varying degree of resistance. Thus far: three of them grow well in a concentration of 25 μg./ml., six in 22 μg./ml., eight in 18 μg./ml., 15 in μg./ml., 16 in 12 μg./ml., 17 in 10 μg./ml., 19 in 8 μg./ml., 20 in 4 μg./ml.

It seems that the *in vitro* resistance will keep on increasing along with the serial passages. Whether or not this will be of a clinical significance in the future will depend on the use of the new antibiotic and not so much on its ability not to be destroyed by penicillinase. It seems that staphylococcal resistance is a more complicated phenomenon and it cannot be so simply correlated with penicillinase-production. We have observed in the past penicillinase-producing Gram-negatives which, despite being sensitive to high concentrations of penicillin G, were clinically useful in urinary-tract infections. Some excellent clinical results in that series were not influenced by penicillinase-production. It might have been due to a different rate of penicillinase-production so that the penicillin may have had enough time to act before being neutralized.[1]

As to the new penicillin, we do not think that it will be handicapped by *in vivo* resistance, for the reasons that Dr. Barber states, but it would be surprising if alone it is the answer to the staphylococcal problem. So far it may prove life-saving, as happened in one of our cases (a fulminating staphylococcal cellulitis of the head in a 1-month-old child), where we experienced a response similar to those of the first days of the penicillin era. It is interesting that novobiocin could not save the child, despite the great sensitivity of the strain towards it.—We are, etc.,

GEORGE K. DAIKOS.
P. KOURKOUMELI-KONTOMICHALOU.
ATHANASIOS PARADELIS.

Department of Clinical Therapeutics,
Athens University School of Medicine,
Alexandra Hospital, Athens, Greece.

REFERENCE

[1] Daikos, G. K., and Athanasiadou, M., *A.M.A. Arch. intern. Med.*, 1959, **104**, 378.

Service Overseas

SIR,—Mr. John Harkness (November 19, p. 1522) has touched on the core of the problem. Men want jobs to which they would willingly devote their lives. For this, three things are essential: (i) They should be able to practise medicine in a way that satisfies their professional standards. (ii) There should be security of tenure. (iii) There should be proper financial rewards with special regard to the problems of the education of the children. The new universities, as the natural guardians of professional and intellectual standards, should play an important part in any scheme such as that suggested by Mr. Harkness.

I have recently returned from a very brief visit to Nigeria, during which I had the opportunity of seeing the excellent secondment arrangements between the Royal National Orthopaedic Hospital and the orthopaedic services of Kano. But I remain convinced that, without the long-term essentials, secondment arrangements are not capable of making anything more than a minor contribution to the problem.

May I take the opportunity to refer to another aspect of the same problem? With the recent final examinations at Ibadan, Africa has begun to turn out itself its own excellently trained medical graduates. Within a few years Nigeria alone will be qualifying 50 doctors a year, soon to be increased to 100 or 150. Many of these will seek postgraduate training in this country. Two courses will be open to them. They may decide to apply for a post in a British hospital, in which case they will come here, take lodgings, apply for posts as advertised, and eventually, after perhaps the disappointment of many unsuccessful attempts, may obtain a post. Alternatively they may sit for a higher degree and spend most of their time here taking theoretical courses of instruction. I would suggest that we in this country need to do two things: (i) Make arrangements whereby properly vouched-for applicants can be placed in properly vouched-for hospitals before they leave their own country. (ii) Institute a new system of postgraduate training comparable to that of North America, in which more stress is laid on properly supervised hospital training and less on examinations. If we do not take some steps on these lines Africans will go elsewhere for their postgraduate medical training, which at present they do not want to do.—I am, etc.,

London W.1. DAVID PATEY.

Drinking Drivers

SIR,—It is very interesting to read in your issue for November 19 two opposite opinions about the importance of nystagmus as a sign of a driver's capability. Dr. J. C. Prestwich (p. 1521) suggests that the sign is either improperly elicited or that the result in connexion with the task of deciding a man's fitness to drive is "an irrelevant piece of evidence." On the other hand Dr. Simon Freeman's observations (p. 1513) on this single factor show a remarkable reliability. It is also my experience that nystagmus is a sign in alcoholic intoxication which appears at a stage where the driver is too much affected by drink for the examiner to give him the "benefit of the doubt."

In a series of cases during the past three years seen as a police surgeon I have figures very similar to those of Dr. Freeman in relation to nystagmus.—I am, etc.,

London E.1 B. D. LASCELLES.

SIR,—As a member of the B.M.A.'s Alcohol and Road Accidents Committee, and as honorary secretary to the Association of Police Surgeons of Great Britain, I feel I must comment on Dr. Simon Freeman's paper "The Drinking Driver" (November 19, p. 1513). Dr. Freeman quotes the B.M.A. Report *Recognition of Intoxication* as stressing the importance of "fine lateral nystagmus" in the examination of drivers suspected of being under the influence of alcohol. Although he later refers to the most recent edition (1958) of the report he does not seem to have realized that the word "fine" has now been omitted. This was the result of a unanimous decision of the committee after a very full discussion during which it was felt that retention of the word "fine" served no useful purpose. For the same reason the card "Notes for Doctors Examining Persons Suspected of Being under the Influence of Alcohol," which was recently published by the B.M.A., also omits the word "fine" with reference to nystagmus.

I am alarmed at the judicial powers which Dr. Freeman appears to adopt in reaching his decision. It is the duty of a police surgeon to examine, to weigh in his mind all that evidence provided by his examination, and to pronounce that in his opinion the suspect is, or is not, fit to be in charge of a motor vehicle. If he cannot make up his mind he should say so, and ask for a "second opinion." Dr. Freeman admits to usurping the functions of the judiciary by himself giving the accused "the benefit of the doubt," even when he would be unwilling to allow himself or his family to be driven by the suspect at the time. To my mind this amounts to an unqualified statement that the suspect was *not* fit to be in charge of a motor vehicle, and a certificate to that effect should be given to the police. It is for the court and not for the police surgeon to award the benefit of any doubt. Every time a police surgeon gives a certificate that a suspect is fit to be in charge of a motor vehicle in circumstances where he would not allow himself or his own family to be driven by the suspect, he runs the risk of himself being accused of giving a certificate the contents of which he knows to be false. —I am, etc.,

London N.19. C. H. JOHNSON.

Treatment of Gastroduodenal Haemorrhage

SIR,—We would like to congratulate Mr. David J. Tibbs on his excellent article "Selective Surgery for Gastroduodenal Haemorrhage" (November 5, p. 1346). Probably the most significant feature he has brought forward is the importance of carrying out gastrotomy or duodenotomy to locate the source of bleeding when necessary.

On the principle that "he who fights and runs away lives to fight another day," it is our inclination in *severely ill* patients to control the bleeding by suture, close the gastrotomy or duodenotomy, and return the patient to bed. Ten or more days later definitive surgery can be carried out. In the appropriate case, we have found better results by this approach than by carrying out major procedures at the emergency operation in all patients.

With regard to disruption of the wound it has been said that surgeons are inclined to make the same mistake three times before they do a thing correctly. We wonder how much disruption is due to the citrate in stored blood? Does it occur when large transfusions are given with fresh blood? In our small experience we think not. We agree with Mr. Tibbs that blind gastrectomy is to be avoided.

We would like to know more of the extent of collaboration between the medical and surgical sides in dealing with this problem. For example, are all cases seen from the beginning by a member of both sides? If not, at what stage is the surgeon asked for advice? What happens to the patient over 40 years with a known peptic ulcer who comes in with a second or third haemorrhage that is controlled by conservative measures, etc.?

These observations are not intended to criticize a very excellent paper on a difficult and controversial problem.—We are, etc.,

S. MOTTERSHEAD.
D. C. DICKSON.

North Ormesby Hospital, Middlesbrough.

SIR,—Mr. David J. Tibbs is to be congratulated on his admirable article on gastroduodenal haemorrhage (November 5, p. 1346). There is one part of it on which I would like to comment—the value of gastrotomy when the origin of the bleeding cannot be detected by external examination of the stomach and duodenum. I endorse completely his comments. I think this obvious manœuvre possibly has not been generally accepted, because if a small opening is made little can readily be seen, unless the bleeding point is on the lesser curve near the incision. Why a small opening? If a gastrotomy wound of three inches or so does not reveal the bleeding point, then open up the stomach until it does.

The last patient on whom I did this was a girl of 12 years, and the bleeding point, an artery, was situated at the very top of the fundus. This was tied and recovery was absolute. The cause of the bleeding remains unknown, but if a blind gastrectomy had been done on this patient nothing would have been achieved. Surely we should stop talking hopefully about a blind gastrectomy and be sensible and look and see. I may be wrong, but I can see no reason at all why the stomach should not be opened, if necessary, with impunity, and since I have practised this I have not failed to find the bleeding point.—I am, etc.,

London W.1. PETER MARTIN.

Prescribing Costs

SIR,—Drs. Alistair Mair, George B. Mair, and Andrew Taylor's article on "A Prescription for the Reduction of Prescribing Costs" (November 12, p. 1442) is fully in accordance with the common practice of trying to prove that good medicine and the National Health Service are incompatible.

In a partnership of three in a small country town our practice has increased by 1,362 patients since April, 1955. With a cottage hospital we have continuous care of nearly all our patients, and no drug is ever withheld on grounds of cost. Our prescribing costs are consistently below the national average, and are approximately the same as those for our area. The following two samples, with national figures in parentheses, are the first and most recent figures available for our practice.

In April, 1955, our average cost per prescription was 3s. 5d. (4s. 4d.), and the average cost per patient was 1s. (2s.). The average number of prescriptions per patient was 0.292 (0.468). In April, 1960, the figures

were: cost per prescription 6s. 10½d. (7s. 1d.), cost per patient 2s. 4½d. (2s. 11d.), and prescriptions issued 0.346 (0.410).—I am, etc.,

Redditch, Worcestershire. C. L. POTTS.

SIR,—One of the major factors influencing the average cost per patient is the geriatric loading of the individual doctor's practice. This has been ignored by the Hinchliffe and Douglas Committees; but I would point out that it completely vitiates the attempt to compare any individual doctor's prescribing with the area average. Not one but four substantial factors are in constant operation: geriatric prescribing is noted for, firstly, an increased number of prescriptions per form; secondly, a repetition of scripts for "maintenance therapy"; thirdly, the increased cost and quantity of the drugs in each prescription compared with such in the younger age group; and, fourthly, a more subtle factor—the increased "patient consulting rate" of this group. Thus, the prescribing costs will be proportional to the geriatric loading in a steeply rising linear curve, so that a moderate overloading will cause a rocketing of the cost. This all-important parameter, the geriatric overloading, cannot be ignored; and it would be a grave miscarriage of their authority if the local medical committee, as a final resort, withheld money from the doctor's remuneration without taking it into account. The geriatric type of prescription begins at age 40.

Drs. A. Mair, G. P. Mair, and A. Taylor (*Journal*, November 12, p. 1442) would do well to make an age–sex breakdown of their practice, and compare it with their national figures. Revealing is their remark: "Even so, a large proportion of our entire practice seems to belong to the chronic-sick group," and that of the regional medical officer "a shockingly high figure." The age–sex register of my own practice has disclosed a 22% geriatric overloading. From W.H.O. statistics published in 1958 the following figures are extracted:

England and Wales, total population, 44,441,000; total over 40, 19,588,000; total under 40, 24,853,000.

Therefore in each 3,000 of the population there are: over 40, 1,322; and under 40, 1,678. In my own practice of 3,000 the figures are: over 40, 1,607; and under 40, 1,393.

I, too, have repeated visits from the R.M.O. I am sure if I went into partnership with Drs. Mair, Mair, and Taylor in the young population of a new council estate we would be commended rather than condemned for our prescribing.—I am, etc.,

Birmingham. F. V. A. BOSC.

SIR,—I found the article by Drs. Alistair Mair, George B. Mair, and Andrew Taylor (November 12, p. 1442) interesting and useful; the "prescription" being facile was never intended for an E.C.10!

One item not mentioned, which will remain very difficult to assess, is the money saved in the benefits not paid owing to an earlier return to work brought about by the use of the more expensive and effective drugs. However, the economic pressures legitimately demand a quicker recovery, apart from this being a basic exercise in medicine.

Also, the expensive treatment acquired from hospital presents a difficulty which is virtually impossible to avoid. There seems to be little emphasis on cost in hospitals' prescribing, and perhaps there is virtue in this, despite the change in emphasis in general practice.

It would be interesting to hear from a group practice where the costs are a similar amount below the average.

Where the balance between cost and the anticipated benefits is struck seems to be largely an individual decision taken each time an E.C.10 is used. Apart from the doctor's sense of discretion and the occasional pricing bureau figures there is little to guide, thank goodness.—I am, etc.,

Headington, Oxford. H. E. WELLS.

Fringe Medicine

SIR,—Mr. Brian Inglis (November 19, p. 1525) is most unfair in classing osteopaths and unqualified practitioners together. Every member of the Register of Osteopaths has to have a four-years training. Dr. James Cyriax's argument (p. 1525) that physiotherapists should be taught manipulation is really only valid if they are taught by osteopaths and, in fact, become osteopaths. Certainly if this was done the average duration of stay of patients in the physiotherapy departments would be reduced by 75%. I have sent literally hundreds of patients to osteopaths and have followed the former up carefully; the results on the whole have been very satisfactory.

Doctors with children who are contemplating medicine would be well advised to let them consider osteopathy instead. The work is extremely rewarding, as it results so quickly in loss of pain and restoration of function. Moreover, there is room in this country for between two to three times as many osteopaths as there are now. They make excellent incomes. As much of their work is physical they have the satisfaction of working in a profession which uses mind and body alike. Have you seen their muscles?—I am, etc.,

Colchester, Essex. M. E. LAMPARD.

SIR,—I hope that Dr. James Cyriax (November 19, p. 1525) will be gratified to learn that at the Annual Representative Meeting of the B.M.A. at Torquay this year a motion "That this Meeting, recognizing the value of manipulation without anaesthesia, urges that medical students should be taught selected manipulative techniques" was carried as a reference to Council (*Supplement*, July 2, p. 11).

This motion stood in the name of the N.E. Suffolk Division, the members of which are disturbed by the failure of almost all medical schools to include the teaching of manipulative techniques in their curricula in spite of the fact that musculo-skeletal disorders, amenable to relief by manipulation, constitute a very considerable proportion of the disabilities for which patients consult their general practitioners. By the same token I hope that Dr. Cyriax's cogent and authoritative letter will carry its full measure of weight when Council come to consider N.E. Suffolk's motion.—I am, etc.,

Southwold. J. C. LEEDHAM-GREEN.

SIR,—Dr. James Cyriax and Mr. Brian Inglis (November 19, p. 1525) imply that there are no medically qualified osteopaths in this country. Nothing can be further from the truth. There are many medical practitioners, like myself, who are also fully qualified osteopaths, and this training is not, as Dr. Cyriax suggests, some slick manipulative technique to be picked up by a medical student in his very brief sojourn in a very busy physical medicine department. On the

contrary it is a subject taught at an intensive full-time course extending over a period of one year.

The reason that patients cannot get free National Health treatment is very simple: hospitals will not appoint medically qualified osteopaths to their staffs. —I am, etc.,

London S.E.24. JOHN H. DAVIDSON.

SIR,—Dr. James Cyriax's letter (November 19, p. 1525) restates some pertinent points about "fringe medicine," and in particular about manipulation. The ideals he aims at are entirely sound, that all effective manual methods should be available to the patient through the National Health Service, and there should be no need for him to seek advice outside the medical profession; but are the physiotherapists competent to do this work? A few are, many try, but the work is by no means easy and in my opinion cannot be taught in the ordinary three-year training of the physiotherapist as it stands to-day.

Dr. Cyriax quotes the developments in Norway, where physiotherapists are doing excellent manipulative work, but he does not point out that these keen students and practitioners have pursued their studies even further, they regularly meet and have postgraduate instruction. Further, they have in large measure abandoned the extra-forcible manipulative techniques which he advocates and have now adopted the gentler and more controlled osteopathic techniques. While it would be entirely desirable for physiotherapists to do this work under medical aegis, it is unlikely to succeed until and unless the physiotherapists are themselves prepared to put in at least two years' study, as the osteopaths do after their preliminary studies in anatomy and physiology, chemistry and physics.

Mr. Brian Inglis of *The Spectator* points out (November 19, p. 1525) that some of the fringe groups have already "put their house in order" and have become organized and reputable. I think he is referring to the osteopaths, who now have a register of competent practitioners who have had a high standard of training and who observe a high standard of ethical professional conduct. This register has now been recognized by the courts of law, and these practitioners should now be recognized by the medical profession so that the public can derive the benefit from their services without having to pay for it, and without having to obtain the treatment in a clandestine manner.—I am, etc.,

London W.1. ALAN STODDARD.

SIR,—Geoffrey Murray's survey of "fringe medicine" in *The Spectator* has raised a number of queries mainly from doctors interested in osteopathy. May I add a few points from a physician practising homoeopathy as an addition to orthodox medical practice?

Firstly, the inclusion of homoeopathic treatment within the National Health Service was not entirely the result of public opinion, but was largely due to the forceful arguments of a few devoted homoeopathic physicians, who knew the value of this form of therapy, and wished to see it made available to the public within the framework of the N.H.S. Secondly, it is surprising to-day how few medical men know that this is the case, and that the hospitals and out-patient departments in London, Glasgow, Liverpool, Bristol, and Tunbridge Wells are available to give advice and homoeopathic treatment to any patient wishing this form of therapy. Frequently patients come privately to see a homoeopathic doctor, because they do not know of the out-patient facilities, or are afraid to ask their own orthodox family doctor to refer them to the clinics or to a consulting homoeopathic physician, knowing that he is antagonistic to this form of treatment.

Surely this type of attitude merely encourages the patient to seek homoeopathy at the hands of one of the many quacks and unqualified homoeopaths who still practise with considerable success in this country. Homoeopathic treatment still has much to offer to those in ill-health, in spite of the advances in orthodox therapeutics, and can be used very successfully in combination with much that is good in modern medicine. Is it not time that old prejudices were forgotten and practitioners encouraged to use all means available to help their patients, either by using homoeopathic remedies in their own practices or referring patients in a friendly manner to a physician with more experience of homoeopathic treatment?—I am, etc.,

Glasgow. H. W. BOYD.

SIR,—In his letter under the above heading (November 12, p. 1457) Dr. Leslie B. Hartley suggests that the "indifferent and increasingly brusque manner of so many National Health doctors" is enabling private practice outside the Service to survive, in spite of the cost of drugs and appliances to private patients. If Dr. Hartley had given reason to assume that he was in N.H.S. practice as well as private medicine, it would have been possible to ask him how far his statement was substantiated by his own experience. Instead one may perhaps inquire through you, Sir, whether other doctors find that it pays them to be unsympathetic to their N.H.S. patients. Presumably it would do so if these patients are driven thereby to become private patients of the doctor concerned or of some other doctor.

I do not think Dr. Hartley's letter would convince any government that it had been wrong not to encourage private practice to a greater extent than hitherto. One is extremely sorry for the patient who feels that he has to put up with rudeness from his doctor because he cannot afford to pay, but is there any evidence that this sort of doctor is going to increase in human kindness by being given a better prospect that bad National Health work is more likely to pay him? A patient able to pay is not going to suffer least at the hand of the bad N.H.S. doctor who knows this. Finally, may one ask why doctors who are for ever pointing out that free drugs and appliances are the due of the heavy taxpayer appear to forget that by the same token the rich patient is entitled to receive free and courteous medical treatment from any N.H.S. doctor? Many will be inclined to agree that bad N.H.S. medicine is keeping private practice alive and conversely it is probably a fact that to some extent absence of private patients in a district is an indication that good medicine is generally available.—I am, etc.,

Eye, Suffolk. J. SHACKLETON BAILEY.

Vacuum Extractor in Obstetrics

SIR,—I was pleased to read the letter of Mr. J. A. Chalmers and Mr. R. J. Fothergill (October 15, p. 1156), but I feel that in some respects I have been misquoted and that my previous communication (August 20, p. 602) has received an incorrect interpretation. In the first instance, my reason for writing was to advocate a greater

use of the vacuum extractor in the first stage of labour, rather than to decry its use in the second stage of labour. I have found that cervical trauma, as a result of the use of the vacuum extractor in the early first stage of labour, is the exception rather than the rule and I consider that Mr. Chalmers and Mr. Fothergill have been unfortunate in their cases. Similarly, trauma to the scalp is usually minimal, and I would suggest that it results more often from oblique traction rather than prolonged traction. Malmström[1] described necrosis at the edge of the suction mark, but stated that it always healed well, and it is interesting to note that some of his cases were submitted to continuous traction for periods of several hours.

At the Royal Society of Medicine I stated that "it was unusual to complete a case in less than an hour." This period would include the time taken to prepare the skin of the perineum, perform pudendal block, and await at least 10 minutes to create the vacuum. Thus it is not correct to say that the "delivery took at least an hour in each case."

Further, I did not advocate a restriction of the vacuum extractor to the first stage of labour as stated by Mr. Chalmers and Mr. Fothergill. I presume they reached this conclusion from the paragraph of my letter which they quoted: "any obstetrician who is reasonably skilled in the use of forceps will find few indications for the vacuum extractor in the second stage of labour." To elaborate on this paragraph I would point out that I think there are a few indications for the vacuum extractor in the second stage of labour: (1) with certain malpresentations, (2) when delivery is considered necessary in a multipara but the high station of the head precludes the use of forceps, and (3) for the beginner, as a means of acquiring experience with the instrument. From time to time a further indication may appear, but all these collectively, in my opinion, may be described as "few." Lastly, the above specific indications are not meant to convey that the vacuum extractor cannot be used for other reasons in the second stage, but merely that it is not as effective a means of delivery in these cases as the forceps. Thus there is no reason why it should not be employed in the problems of domiciliary practice.

—I am, etc.,

The Rotunda Hospital, Dublin. E. W. LILLIE.

REFERENCE

[1] Malmström, T., *Acta obstet. gynec. scand.*, 1954, **33**, Suppl. 4.

Androgenic Potency of Fluoxymesterone

SIR,—Fluoxymesterone ("ultandren") was used by Buckle[1] in the treatment of 10 cases of eunuchism and male hypogonadism in the endocrine clinic at St. Bartholomew's Hospital.

All except one were transferred to fluoxymesterone from previous treatment with oral methyl testosterone. The exception was having testosterone propionate implants—400 mg. every four months. Nine of the ten responded satisfactorily to fluoxymesterone, 2.5 mg. daily, during a period of observation of two to six months, including the case previously treated by implantation. At New End Hospital we have treated nine patients with fluoxymesterone:

Group I consisted of four patients, all with an abnormally low excretion of 17-ketosteroids. Two suffered from congenital hypogonadism, one from acromegaly with hypogonadism, and one, a man of 46, from impotence. The first three required daily doses of 3 to 5 mg. of fluoxymesterone, the last 14 mg. All had previously been maintained satisfactorily by means of 500 mg. of testosterone implanted every six months. They were observed for 14 to 17 months while under treatment with fluoxymesterone.

Group II consisted of a patient with impotence and a low excretion of 17-ketosteroids, previously maintained by 700 mg. of testosterone implanted every six months for two years. He required 30 mg. daily to maintain sexual performance for three months, when he relapsed. Further implants were successful.

Group III consisted of a hypogonadal patient 20 years of age who had not previously received implants. He became sexually normal when treated with 2 mg. daily of fluoxymesterone.

Group IV consisted of three patients whose treatment was not maintained. One defaulted from lack of enthusiasm, one because of his distance from the hospital, and one because he had previously been treated with fluoxymesterone unsuccessfully and did not wish to try it again.

Buckle found that in his series of 10 patients the potency of fluoxymesterone was 7.5 to 15 times that of methyl testosterone. This probably implies a potency of about 1.5 to 3 times that of implanted testosterone. In the present series of five patents, all of whom had been treated previously by implantation, the potency of fluoxymesterone was disappointingly less. The patients had previously received approximately 2.75 mg. daily from their implants. They needed a dose of 2 to 14 mg. (and in one case 30 mg.) to achieve potency. In the last case even this dosage failed to maintain potency and implantations were resumed. Buckle commented on the absence of oedema in his series. No evidence of water-retention or of other undesirable effects occurred in our series, but one patient, not included, who, on his own initiative, adopted a dosage of 50 mg. of fluoxymesterone daily, developed massive oedema and was sufficiently frightened by this effect and disappointed with the results to accept thereafter the sexual inactivity which his age justified.

I am grateful to Dr. Raymond Greene, under whose guidance this trial was performed, for permission to publish the results.

—I am, etc.,

New End Hospital, London N.W.3. D. F. RIDEOUT.

REFERENCE

[1] Buckle, R. M., *Brit. med. J.*, 1959, **1**, 1378.

Treatment of Leprosy

SIR,—Though a full-time worker in leprosy for only four years, I must nevertheless take up cudgels with my former mentor Dr. Robert Cochrane (September 17, p. 860) for accusing your leader writer (August 27, p. 655) of "distorting the picture quite considerably." I just cannot understand why Dr. Cochrane prognosticates so gloomily about dapsone and the other new drugs when there is now ample clinical evidence throughout the world of their efficacy. However, in this letter I shall refer to results in Bali alone.

He states that 50–75% heal spontaneously. Of course we all know that, as tuberculoid cases normally have a high immunity. But what of the lepromatous ones with low or no immunity, and tuberculoid ones that go into reaction, resulting, without treatment, in permanent damage to the nerves? Formerly all these were doomed to progressively advancing mutilations which, when sufficiently repugnant, caused them to be thrown out of their villages as outcasts, unless early death from malnutrition or concurrent illness mercifully intervened. Now dapsone has completely changed

the picture, and every new patient can be assured that such a fate will never be his.

Here in Bali the contrast between the pre- and post-dapsone patients is most striking. All the former—300 of them—who were not lucky enough to be in Dr. Cochrane's group to heal spontaneously have now been gathered up to live in six leprosaria by the sea, clothed and fed by the government. Practically all of them have revolting and pathetic mutilations. In marked comparison are the 2,000 out-patients who are making dramatic progress under dapsone. This they receive regularly at a set time and place every two weeks at one of 90 different places throughout the island; it may be in a bamboo and coconut-leaf shelter, or under some trees, or just by the roadside. Not only is ugly infiltration receding, but to all intents and purposes the development of contractures and mutilations is now a thing of the past. Moreover, and this is of vital importance, almost 100% are still fully accepted members of the community: not one has been hounded out of his normal occupation. Within the last two years, patients have been allowed to join in the communal rice gathering, for example, and carpenters are flooded with orders for work. A further objective proof of the efficacy of dapsone is that also within the same period 500 of our present patients have presented themselves *voluntarily* for treatment, and the great majority of these are in the earliest stages without deformities having already developed, and this because Bali has seen with its own eyes during the previous two years the results of dapsone. No wonder we here, together with your leader writer, can look forward to the future with cheerful confidence.

The paradox is that such good results with negligible toxic effects are entirely due to the discovery of Drs. R. G. Cochrane and John Lowe that induction with dapsone should be, not with 28,000 mg. a week as in 1943, but only 50 mg. And that small dose can be given to a semi-advanced lepromatous case for a year with the most wonderful results. Certainly dapsone may have to be taken for 20 years or more. But what is that to a patient who no longer is an object of loathing? Certainly 10% may remain bacillary positive for many years. But what of that? The patient can easily avoid close contact with children and his family, allowing for the fact that the bacillus remains virulent, which is doubtful. Certainly a proportion will develop reactions. But all these can quickly be brought into a central ward, where rest to swollen nerves and other treatment that Dr. Cochrane himself so ably advises will in almost all cases lift the patients over this hurdle. One can now say that no reaction case properly treated should develop permanently damaged nerves.

Dr. Cochrane does indeed admit that "modern treatment has revolutionized the whole outlook of the disease," but paradoxically continues that this "has made possible the great advances in orthopaedic surgery and plastic surgery," but I would like to make the point that it is the *neglect* of the use of modern drugs that alone had made this advance possible, giving the surgeons much fodder.

W.H.O. have recently requested leprologists to give them a return of all patients, grading every deformity from anaesthesia to advanced mutilations, especially noting the effect of drug treatment. They ask this because they contemplate a world-wide rehabilitation scheme. I am therefore now in the process of so re-examining all our out-patients, and it is already certain that my statistics will show that, in a field campaign where practically 100% of patients are getting treatment regularly, there is no need for such a costly scheme as there would be so few to rehabilitate.—I am, etc.,

Ben Pasar, Bali, Indonesia. SPENCER REED.

SIR,—Mr. D. P. Choyce has brought up an interesting point in his letter (September 10, p. 797) in that, while leprosy is being eliminated as a systemic disease, the eye complications are still being recorded. This is hardly a clinical cure. I feel sure the damage is done by the time the patients get to London, having presumably contracted the disease in the Orient or Pacific regions. While in the South Pacific for two years, living among the lepers, so to speak, I had occasion to see the disease in its early state at close quarters at Suva before being sent to the colony at Makongai.

Early atropinization is the only weapon to slow down, not prevent, the uveitis which is so destructive of vision in this disease, and if it is used daily for the first six months of the disease there will be a major saving of vision later on. The antibiotics and cortisone are useless locally and are contraindicated; gutt. "solutox," and gutt. atropine 1%, are worth intensive trial and there is no need to fear atropine irritation, etc., as the skin of the face and lids is frequently anaesthetic.

With regard to the late complication of cataract in these leprotic cases, there are a few points of general interest. It is possible to remove the lens without local anaesthesia as the patient feels no pain in cornea and iris. This is only done of course if there is useful light-projection, which there frequently is not, and applies to selected cases, to give the patient a greater visual field if warranted. Often the uveitis is not central and the patient can sometimes read after cataract surgery. The leprotic pannus of the cornea is somewhat more dense than that of trachomatous pannus, and so it is worth eliminating the lens by the inferior route incision as frequently there is a recrudescence of pannus, as I learned to my horror several times, if the lens is removed superiorly—that is, with Graefe's knife, not keratome. Naturally also it has to be an extracapsular extraction, as frequently synechiae, etc., do not give one much room. This is combined with a large iridectomy.—I am, etc.,

Perth, Western Australia. P. J. DALY.

Smoking and Disease

SIR,—Your annotation, "Smoking and Disease" (October 8, p. 1077), directs attention to the hazards of cigarette-smoking and to the increasing awareness of their serious nature and extent. As you put it, the time is ripe for more effective preventive action than has so far been taken. In response to a request by the Government in 1957 that local authorities take all measures to make known to the public the dangers of cigarette-smoking, Edinburgh, over a period of three weeks, carried out an intensive campaign during which, incidentally, 30,000 copies of the B.M.A. publication, *Smoking—The Facts*, were distributed at meetings and to schoolchildren. The results, unfortunately, were in no way commensurate with the very great effort made. Almost the only encouraging outcome was a hardening in the public attitude towards smoking by young people. Nearly ten years have passed since the causal association between cigarette-smoking and lung cancer was established, and there is to-day no justification whatever for failing to take all possible measures to protect our young people from the dangers involved. The manufacturers now spend £5m. annually advertising their products, and our youngsters are continually exposed to the most subtle and pervasive propaganda.

In his report just published,[1] the Chief Medical Officer of the Ministry of Health records that the total deaths from lung cancer are now the highest so far recorded and that the number of deaths from coronary artery disease, which now more and more is believed to be closely associated with cigarette-smoking, was also greater than in any previous years.

It has been shown in Edinburgh that even the most efficient municipal endeavour is not enough and that a high-level national effort is required to deal with a habit so closely woven into the social life of the community. In the words of the Tuberculosis Council report, quoted in your annotation, "we are faced with a health problem of great magnitude, and not enough has been done centrally to safeguard the public welfare." There is surely something wrong about a national ethic which permits the unrestricted advertisement of a product so dangerous to the public health.—I am, etc.,

Edinburgh 9. S. LIPETZ.

REFERENCE

[1] *Report of the Ministry of Health for the year 1959. Part II. On the State of the Public Health, Being the Annual Report of the Chief Medical Officer*, 1960. Cmnd. 1207. H.M.S.O., London.

White Mouse Medicine

SIR,—I do not wish to trespass further on your columns in pursuit of what is, after all, a private squabble, but there is one point in Dr. Hugh Sinclair's letter (November 19, p. 1520) over which I owe him an apology and an explanation. He says (of my article), "Another remarkable statement is that Americans eat far less butter than any other race in the world." The figures are as follows.[1] I set them against the figures of deaths from arteriosclerosis and degenerative heart disease in the year 1956.[2]

Country	Percentage of Deaths to Population from Arterio-sclerosis and Coronary Disease	Estimate per Caput Consumption of Butter (lb.)
U.S.A.	0·325	8·8
U.K.	0·279	15·6
AUSTRALIA ..	0·266	29
SWEDEN	0·256	19·2
NEW ZEALAND ..	0·231	43·1
CANADA	0·227	20·5
DENMARK	0·214	19·6
FINLAND	0·209	26·9
NETHERLANDS ..	0·190	6·4
NORWAY	0·183	7·1
GERMANY (West) ..	0·181	15·4
FRANCE	0·061	24·5
JAPAN	0·047	—
POLAND	0·024	—

It will be seen that two countries, Holland and Norway, eat slightly less butter than the U.S.A., for the supply of butter to butter-starved Europe is one of their chief exports. America leads the field easily in coronary disease.—I am, etc.,

London W.1. HENEAGE OGILVIE.

REFERENCES

[1] *Commonwealth Economic Committee Intelligence Bulletin for the Year 1956*, 1960, vol. 13, No. 1, p. 22.
[2] *United Nations W.H.O. Survey for the Year 1956*, 1959. W.H.O., Geneva

SIR,—Dr. Hugh Sinclair (November 19, p. 1520) is a fervent believer in fats as a cause of cardiovascular disease—like many Americans. Modern man, he opines, is unable to survive on contemporary diets.

Heredity, exercise, steroids, occupation, smoking, overall obesity, stress—and indeed a person's total way of life—can all be held to contribute to the growing incidence of coronary thrombosis, particularly that which occurs in men before retiring age. Rather than fulminate about our own "beliefs" in this matter, we should take notice of what Sir Howard Florey recently so succinctly said in your columns (November 5, p. 1329)—that we really know very little about the cause of this disease. Having recognized this, and being biologists, we might usefully go on to make a mental note that it is, on the whole, unlikely that a condition like this will eventually be shown to have a single cause. In the meantime, we must protect the public from the dogmatic nostrum-pedlars who have proved their case to their own but not to the general satisfaction.

In this respect, my experience of the manufacturers, particularly the food manufacturers, is more in accord with Sir Heneage Ogilvie's, than with Dr. Sinclair's, experience of them. Just before President Eisenhower's visit, I was subjected to a fair amount of pressure to support a low-fat food which claimed a considerable stake in his survival. In my view, we must preserve an open mind about the aetiology, and indeed the "modality," of atherosclerosis until some really convincing evidence about its cause and prevention is produced.—I am, etc.,

London S.W.1. H. BERIC WRIGHT.

SIR,—I am sure that Sir Heneage Ogilvie never meant to castigate all laboratory experiments, but only those that try to prove the impossible. Evolution clearly indicates, for example, that failure to exchange the fat in the milk, beef, and mutton of the Old World for such a material as the sunflower-seed oil of the New can never be the basic cause of coronary disease in white races, and experiments in unnatural substitutions are doomed strategically from the start. As I said in my correspondence with Dr. Hugh Sinclair on this subject in the *Lancet* last year,[1] how can the tree turn out to be right if the wood can be proved to be wrong? Hunter's "Why think, why not try the experiment?" could often be better put the other way round.

Should it be argued that these unnatural substitutions apply only to treatment, how illogical to make the dietetic treatment of coronary disease differ from its dietetic prevention! Three months ago I pointed out in your columns[2] that castigations of natural fats are completely at variançe with the earliest teaching of the Old Testament,[3] which historical fact shows the illogicality of blaming on such ancient foods the present high incidence of coronary disease.

I note that Ancel Keys[4] now tries to get out of the conflict with evolution by stating, *inter alia*, that there was never as much fat available in bygone days as there is to-day. He forgets that Nature reacts to a natural food surplus not by the production of disease but by rapid multiplication. If mankind eats relatively unaltered fats from his age-long environment, and accurately consults his appetite, he will be just as safe in a world with plenty of these as a pigeon in ten acres of wheat or a *Bacillus lactis* in a pound of butter.

As regards references on the subject, there are now over 2,000 available, many in opposition to each other. Perspective on these has been supplied by J. Yudkin.[5] I do not myself see how exercise can have as much prophylactic value as Sir Heneage ascribes to it in coronary disease, but if excess fat consumption be the basic cause, which of course remains problematical, there is no need to indulge in unnatural substitutions to obtain salvation. The excess can be dealt with, as I have tried to show in my small work,[6] by attacking the

sophisticated food mixtures of our present civilization, such as chocolate, ice-cream, and many others, where fat is not properly subjected to the discrimination of the tongue but is smuggled into the body under a host of cloaking materials.—I am, etc.,

Lee-on-Solent, Hants. T. L. CLEAVE.

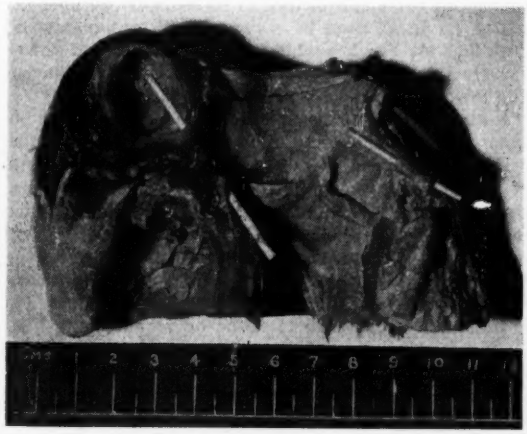
REFERENCES

1 Cleave, T. L., *Lancet*, 1959, **1**, 365, 632.
2 *Brit. med. J.*, 1960, **2**, 465.
3 Genesis xviii. 8 ; and Deuteronomy xxxii. 14.
4 Keys, Ancel, and Keys, Margaret, *Eat Well and Stay Well*, 1960, London.
5 Yudkin, J., *Lancet*, 1957, **2**, 155.
6 Cleave, T. L., *Fat Consumption and Coronary Disease*, 1957, Bristol.

Coronary Aneurysms

SIR,—The paper by Drs. Gilbert Forbes and Andrew Bradley (November 5, p. 1344) on coronary aneurysms prompts us to record one seen here recently which was probably atherosclerotic in origin.

A married woman of 70 was admitted on July 1, 1960, having collapsed in the street with severe retrosternal pain. There was a past history of rheumatic fever in childhood ; she had been epileptic since the age of 20 and hypertensive for years. There was also a history of diarrhoea with passage of blood. On admission she was cold, cyanosed, sweating, and stuporous. B.P. 60 mm. Hg systolic, pulse 76 with feeble volume, heart sounds soft with no murmurs



heard. E.C.G. showed minimal changes suggesting a posterior-wall infarction, and because of the severe chest pain she was treated with anticoagulants. The hypotension did not respond to vasopressor drugs and she gradually became more deeply unconscious, dying 30 hours after admission.

At necropsy there was a large haemopericardium which came from a ruptured aneurysm 2 cm. diameter commencing 1 cm. from the ostium of the right coronary artery (see photo). There was generalized atheroma throughout the right coronary artery, including the wall of the aneurysm, which was thin. Proximal to it the lumen of the artery was of normal calibre, but distally it was narrow and the wall thickened. The left coronary was also atheromatous but patent, and there was no evidence of old infarction, the myocardium being soft and pale throughout. There was a small accessory right coronary artery which passed down in the anterior wall of the septum, displacing the anterior descending branch to the left. Other findings included a mild ulcerative colitis and a small subpleural adenochondroma. Microscopically atherosclerotic changes with disruption of the internal elastic affected all coats of the aneurysm and of the rest of the coronary tree. These findings make us reasonably certain that the aneurysm was atherosclerotic.

In retrospect the anticoagulant therapy (heparin and phenindione) probably worsened her condition, as the initial collapse was almost certainly due to the rupture of the aneurysm. This again raises the difficult problem of diagnosing haemopericardium and of the advisability of anticoagulants in suspected myocardial infarction—see the letters from Dr. Ezeka E. Okafor (October 15, p. 1159) and Dr. William G. Smith (November 5, p. 1385).—We are, etc.,

J. C. BURNE.
J. HART.

River Hospitals,
Joyce Green,
Dartford, Kent.

Serum Transaminase in Aortic Aneurysm

SIR,—I read with great interest the article by Drs. Peter Adams and Edna M. Jacoby entitled, "Serum Transaminase Activity of Dissecting Aneurysm of the Aorta" (October 15, p. 1131). May I also quote a similar observation of mine[1] where high transaminase value was associated with dissecting aneurysm of the aorta ?

A 59-year-old male, a known hypertensive and known to have an aneurysm of the ascending aorta for about ten years, presented to me with severe retrosternal pain and features of shock. On examination he was restless, cyanosed, his pulse was 90/minute, B.P. 90/60 mm. of Hg, respiration 24/minute, temperature 101.6° F. (38.8° C.), and his heart sounds were hardly audible. His liver was palpable two fingers below the right costal margin. Laboratory studies revealed Hb 15.2 g., W.B.C. 14,600 with 81% polymorphs, blood urea nitrogen 41 mg., S.G.O.T. on admission was 2,075 units and the following day fell to 326 units. S.G.P.T. was 354 units on the second day after admission. E.C.G. on admission revealed premature ventricular contractions and ST depression with inverted T waves in leads V4, V5, and V6. We treated this patient as a case of myocardial infarction although we thought of dissecting aneurysm as a second possibility.

The patient died on the third day after admission to hospital. A post-mortem examination revealed the following features: Massive haemopericardium. Ascending aorta was uniformly dilated. There was an internal tear 3 cm. long located 3 cm. above the aortic valve. There was a medial dissection localized to a segment of 6 cm. above and below the internal tear. The heart showed the coronary arteries to be patent, but markedly narrowed by atheromatous plaques. There was no evidence of a recent myocardial infarction. The liver was enlarged moderately and had diffuse central congestion and small amount of parenchymatous degeneration.

The presenting features of this patient with high transaminase value suggested a myocardial infarction, although at post-mortem examination it was found to be incorrect. Our impression is that the high transaminase value in this case was due to the dissecting aneurysm, from haemolysed blood in the aorta and pericardial cavity. (Whole blood haemolysates have ten times the transaminase activity of normal sera.[2]) We feel that increased transaminase activity should not be considered an unequivocal basis for differentiating between myocardial infarction and dissecting aneurysm of the aorta, two entities that are so often clinically indistinguishable.—I am, etc.,

Springfield Hospital,
Grimsby, Lincs. N. K. MAJUMDAR.

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1 Majumdar, N. K., and Covo, G. A., *N.Y. St. J. Med.*, 1960, **60**, 3313.
2 Karmen, A., Wróblewski, F., and LaDue, J. S., *J. clin. Invest.*, 1955, **34**, 126.

Salicylate Poisoning

SIR,—Your annotation dealing with the subject of salicylate poisoning is opportune (October 22, p. 1216). The most dramatic recovery from aspirin poisoning I have ever seen concerns a woman aged 35 who ingested 350 grains (23 g.) of aspirin and was found lying in the fields some 36 hours later, at which time her respirations were 40 per minute and she was comatose. Her condition responded dramatically to the intravenous injection of one pint 1/6 molar sodium lactate.

Is it entirely correct to suggest that the value of sodium lactate in cases of salicylate poisoning consists principally in the provision of the sodium radicle? Or is it better and more true to say that the sodium lactate acts as a buffering solution capable of dealing with any respiratory alkalosis but especially any oncoming or actual metabolic acidosis? What seems certain is that very little pooled knowledge exists on this topic and this I believe is due to the fact that the majority of persons attempting suicide utilizing salicylates either are out of danger by the time medical aid is summoned or they are found dead on arrival. The intermediate zone is occupied by comparatively few patients of whom, in turn, possibly a significant number will live in consequence of stomach washouts. It is the residue of this intermediate group of which my patient is the only one of three cases occurring at this hospital during ten years to recover; the other two died.—I am, etc.,

Hill End Hospital, St. Albans, Hertfordshire. HAROLD PALMER.

Serum Leucine Aminopeptidase

SIR,—With regard to the paper by Dr. A. L. Miller and Miss Laura Worsley (November 12, p. 1419) on the diagnostic value of serum leucine aminopeptidase in carcinoma of the pancreas, it should be noted that Harkness *et al.* (June 11, p. 1787) also obtained similar results with their test. It would, however, be a pity to abandon the test completely, for Bressler and Forsyth[1] showed that it was useful in the detection of hydatidiform mole. Incidentally, for those seeking a simple confirmatory test for pancreatic carcinoma, the paper by Okumura and Spellberg[2] on serum isocitric dehydrogenase may be of value.—I am, etc.,

Morriston Hospital, Swansea. E. B. LOVE.

REFERENCES

[1] Bressler, R., and Forsyth, B. R., *New Engl. J. Med.*, 1959, **261**, 746.
[2] Okumura, M., and Spellberg, M. A., *Gastroenterology*, 1960, **39**, 305.

Identification of Drugs

SIR,—Owing to the ever-increasing number of drugs in daily use, may I suggest that all manufacturing chemists illustrate them in their brochures, showing actual size, shape, colour, and any other means of identification?—I am, etc.,

Leeds 8. DAVID A. HERD.

Personal Record Cards

SIR,—When a practitioner is deciding whether to give tetanus antitoxin to a patient for whom no personal record card of previous immunizations is available, it should not be overlooked that information on the immunization state of local children may be obtainable from the M.O.H., with whom immunization records are lodged. An increasing number of infants have been receiving tetanus immunization by means of triple antigen for several years in some areas, and a telephone inquiry to the M.O.H.'s office may avoid the unnecessary administration of tetanus antitoxin.—I am, etc.,

Plymouth, Devon. G. B. CARTER.

Sewage in the Sea

SIR,—With reference to Dr. F. A. Belam's letter (November 12, p. 1457) I offer him £1 to a button that neither he nor anyone else can name 10 sewage outfalls into the sea around this country which conform to the standards set out in his paragraph (6). In fact, I doubt if there is even one.

A point that seems to have been neglected by investigators is the part played by seagulls. These are ever present. At one outfall I know, which is governed by a lunar clock, one can observe the time of discharge by the massing of gulls. Has anyone investigated the fate of pathogenic organisms in the gut of these birds?—I am, etc.,

Area Health Office, Truro. V. E. WHITMAN.

SIR,—Dr. F. A. Belam is to be applauded for his energy and drive as indicated in his letter (November 12, p. 1457). In 14 days he visited 25–30 seaside resorts, inspected all beaches and sewage outfalls, had interviews with medical officers of health, borough engineers, and town clerks, and considered complaints.

It might be interesting to know if he also took random water samples at the sewage outfalls or checked the tide drift from these outfalls. Or if he measured the length of the outfall pipes in relation to prevailing currents. Or if he was satisfied with the working of macerating stations—where installed. Or if he confirmed that existing sewage pipes are of sufficient capacity to accept both sewage and rain-water. Or if he visited the beaches soon after dawn before they had been cleaned up. Or if he had the assurance to bathe on an incoming tide. Or if he spoke to anybody other than officials of the various corporations.

I suspect that this is the town, to which he refers, with a £3m. scheme to divert all sewage from the sea. The first, and most important, stage of this scheme is now well under way, which would indicate that not all councils are so happy about the situation as Dr. Belam would appear to be. It is to be hoped that other seaside towns will follow the lead of this progressive council.—I am, etc.,

Bournemouth. ALAN OGDEN.

Earliest Age for Walking

SIR,—Some excitement has been occasioned in this borough by publication in the local press of a report concerning a male child who walked without assistance at the age of 27 weeks. He is the youngest of six children. No member of my staff can recall a child walking at such an early age, and I wonder whether it is as unusual as it appears.

Perhaps the publication of this letter in the *Journal* will bring to light other authenticated cases of early walking. It would be interesting to know whether this was associated with the passing of other milestones and with exceptional ability in later life.—I am, etc.,

Health Office, Wigan. J. HAWORTH HILDITCH.

Obituary

A. CAMPBELL WATT, M.B., Ch.B., M.R.C.P.Ed.

Dr. A. Campbell Watt, who practised as a neurologist and neurosurgeon in Johannesburg, was killed in a road accident on October 28 while on his way to visit a patient. He was 45 years of age.

Andrew Campbell Watt was born in Germiston on February 23, 1915, the son of Dr. Andrew Hutton Watt, who came to South Africa just after the war of 1900 and was one of the founders of the Chamber of Mines hospital at Cottesloe, Johannesburg. Educated at St. John's College, Johannesburg, and at Haileybury College in England, he studied medicine at Edinburgh University, where his father had held the post of assistant to Sir Harold Stiles before he emigrated to South Africa. He graduated M.B., Ch.B. in 1938, and became a Member of the Royal College of Physicians of Edinburgh in 1947. During his university days he held the Conan Doyle scholarship, and after graduation he held posts in the psychiatric and casualty departments of the Edinburgh Royal Infirmary. Deciding to take up neurology as his career, he became an assistant to Mr. Norman Dott, as he then was, in the department of neurosurgery of Edinburgh University, working there from 1939 to 1943. Shortly before the invasion of Normandy he joined the late Sir Hugh Cairns at the Head Injuries Military Hospital near Oxford. When the invasion of Europe took place he landed in Normandy on D+1 day as the neurologist to a mobile neurosurgical team, and after the war he returned to the Hospital for Head Injuries, which had by then expanded and moved out to Wheatley, near Oxford.

In 1948 he returned to South Africa and became a lecturer at Witwatersrand University and neurologist to the Johannesburg General Hospital. He worked as a member of Mr. R. Krynauw's neurosurgical unit, and on Mr. Krynauw's retirement he played a prominent part in keeping the neurosurgical unit intact during a difficult period. In spite of his hospital activities and a very busy consulting practice he found time to visit the Baragwanath and Coronation non-European hospitals once a week until a full-time neurosurgical department was established to provide a service for these patients.

On his mother's side Andrew Watt came of a long line of lawyers, so that it was natural that he should take a great interest in the forensic side of his work as a neurologist. In the law courts he quickly established a reputation as an expert witness, and his opinion was widely sought by his legal colleagues. He appeared in many famous law cases during the past ten years, and was a founder member of the Medico-legal Society of Johannesburg. He made original contributions to medical literature on head injuries, hallucinations, and alcoholism.

His widow and a son and a daughter survive him.

Colleagues in Johannesburg write: With the death of Dr. Andrew Campbell Watt, not only has the medical profession in South Africa lost an outstanding and talented figure, but many people both here and in Britain have lost a true and esteemed friend. Apart from his academic and professional attainments Andrew had a warm humanity and a generous nature that endeared him to those of us who have known and worked with him. Anyone in trouble could always depend on a sympathetic and practical approach to his difficulties, and no one who asked for his help ever came away without it. He was a man of profound culture, widely read, and with an unusual command of the English language. On occasions his manner was gruff and abrupt, but he had a puckish sense of humour, and nothing gave him more pleasure than deflating pomposity, but this was done in a manner which few of his victims resented for any length of time. His untimely death leaves a gap in the ranks of the medical profession of South Africa which will not easily be filled.

Professor NORMAN DOTT writes from Edinburgh: The tragic and untimely death of Dr. Andrew Campbell Watt focuses attention on Britain's wartime debt to those young doctors of the Commonwealth who threw all they had into service with her medical profession during the stress of war. His father had received his medical education in Edinburgh and had become an important figure in medical circles in Johannesburg. He had sent his son back to the "old school," where he graduated in 1938. The outbreak of war in September, 1939, found Andrew Watt house-surgeon in the department of surgical neurology of the Royal Infirmary, Edinburgh. A few months later the department was moved, for strategic reasons, to Bangour Hospital, near Edinburgh, and Watt moved with it—indeed, one might more properly say he moved it. In those days all available young British doctors were being rapidly recruited for active military service. Dr. Watt dealt with a most formidable task as resident surgeon in the Edinburgh brain injuries unit established at Bangour. He carried a load—about 900 admissions of major neurological injuries and diseases annually and 350 major neurosurgical operations—as single-handed resident surgeon, that would have required at least four residents in peacetime. He displayed extraordinary stamina, energy, and capacity in organizing the emergency unit—about half civilian and half armed-Forces cases. His loyalty to his patients, to his colleagues, and to the high standards of practice he had acquired was magnificent. During the war we were able not only to maintain standards but to improve on them—developing cerebral angiography, treatment of aneurysms, epilepsy, etc., and greatly improving the management of head injuries and rehabilitation measures. That surgical neurology in Edinburgh came out of the war with a larger potential for good and with improved standards of practice was due to Watt's magnificent work during those most difficult years 1940 to 1943. I estimate that he averaged an 18-hour working day—and night—in that period.

Having achieved this, and the unit having become stabilized under war conditions, Andrew Watt felt the call to personal military service at the active fronts, and also to marry. He joined the R.A.M.C., and with his special experience he was posted to the principal neurological military hospital in England, near Oxford. There he served with the principal neurologists and neurosurgeons—Brigadier-Generals Hugh Cairns and George Riddoch, and Air Vice-Marshal Charles Symonds. He was posted as neurologist with a mobile team with the Normandy invasion forces, and acquired fame for his extraordinary capacity for maintaining high standards during sustained efforts. He could do three men's work and do it better than three men. After the Armistice he was stationed in Belgium for a considerable period, and came under the influence and gained the friendship of Ludo van Bogaert, the great neurological figure at Antwerp. He stayed with us for two years after the Armistice—helping to clear up the neurological aftermath of war and finding time and academic capacity to pass the M.R.C.P.Ed. examination in 1946.

His subsequent career as neurologist in Johannesburg again required much of his enthusiasm and pioneering spirit, as surgical neurology was developing there and required his strong support, which he freely gave. He had attained a position of great influence, importance, and respect, and at the age of 46 his potential for good was enormous. At this point, and in the course of responding to an emergency call, comes his untimely end. The loss of this able and experienced specialist is a grievous one to his colleagues and his profession. The loss to those many of us in Britain who were deeply in his debt, who knew his strong friendship, his quiet humour, his grasp of medical and human affairs, his high ethical standards, and his selfless devotion to his patients, is truly tragic. Our deepest sympathy goes out to Mrs. Watt and to his young

daughter and son. We are grateful for the memory of such a loyal comrade, and we are devastated by his untimely death.

E. A. ROVENSTINE, M.D., Hon.Sc.D.

Dr. E. A. Rovenstine, professor of anaesthesia at the New York University Medical Center, died at his home in New York on November 9 after a long illness. He was 65 years of age.

SIR ROBERT MACINTOSH writes: With the death of Emery Andrew Rovenstine, the field of anaesthetics has lost an outstanding personality. Of mixed Dutch and Italian descent, he was born in 1895 at Atwood, Virginia, where for 54 years his parents kept the village store. Early he learnt to fend for himself, earning and learning as he went along—and this, no doubt, heightened his natural determination, resilience, and sense of fun. As a student he waited at table, played professional football, acted as a cucumber-buyer for Heinz, fired furnaces, and worked in a drug-store; and in later years, over a rye-and-soda, he delighted to recount his experiences. Soon after graduating in 1928 he became interested in anaesthetics, and, being satisfied with nothing but the best, found his way, in 1927, to Wisconsin, to be accepted by Ralph Waters as one of his gifted enthusiastic pioneering team. He was closely associated with the introduction of cyclopropane, administering it to his chief, for the first time in humans. In 1935 he was appointed professor of anaesthesia (for this was before anaesthesiology) of New York University, and head of the department of anaesthesia in the Bellevue Hospital, where he became responsible for over 20,000 administrations annually. There can be few British anaesthetists who have passed through New York who have not profited from his teaching and enjoyed his delightful hospitality.

A glutton for work himself, "Rovey" didn't spare his assistants, who were advised not to worry about pay since they were unlikely to have time to spend it. They were well taught, however, and he took great pains to place the deserving ones. He yields only to Ralph Waters in the number of pupils who have attained distinction, and great was his pleasure in their achievements. In recent years he had concentrated on nerve blocks for therapeutic purposes, and accepted invitations to speak on this subject throughout the world, thus happily indulging his passion for travel. On these occasions he was accompanied by his wife, Jewel, to whose understanding and encouragement he owed so much.

Medical Notes in Parliament

STAFF SHORTAGE IN HOSPITAL SERVICE

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Lord STONHAM, who is chairman of the hospital group in the North-West Metropolitan Region, called attention on November 22 to the fact that physiotherapist staffs in the region were 32.7% and psychiatric social workers 31.4% below establishment, and that there was an almost equally acute shortage of radiographers, pharmacists, and almoners. He stated that the position had greatly worsened since the beginning of the year, and asked the Government what they would do to effect an improvement. Lord NEWTON, the Government spokesman, said they were aware that many hospital authorities found difficulty in filling their establishments. These professions were in competition with a number of others, inside and outside the Health Service, and there were not enough young people of suitable calibre to fill all the available posts. Recent figures of student recruitment for training in the Health Service were encouraging, and where specific difficulties—such as inadequate training facilities—hampered recruitment, the Government were prepared to consider how they could help. Salaries were a matter for the appropriate Whitley Council, but the salaries of all the classes mentioned had been substantially increased in the past two years.

Lord STONHAM declared that in spite of the increased salaries conditions were now disastrous. Vacancies had increased by 50% since the beginning of last year, and in some instances had doubled. Unless something radical was done the Hospital Service would be seriously impaired. Lord NEWTON said the Government were only too anxious to help in any way they could to solve the difficulties, and would welcome any suggestions. Lord AMULREE suggested that the salaries should be made more commensurate with what young girls could earn in commerce. The EARL OF LUCAN also mentioned the point about better-paid employment in industry. Lord NEWTON attributed the wastage largely to marriage. In none of these groups was there a general salary claim before the appropriate Whitley Council. The trouble was that if salaries were increased substantially they would be matched by increases in the competing professions. Lord STONHAM assured him that the trouble was not marriage but salaries. The main obstacle was that the Whitley Council machinery had virtually seized up. Lord MCCORQUODALE OF NEWTON suggested that part of the difficulty was the extension of the amount of knowledge to be acquired before the appropriate degree or qualification could be obtained, and that a less skilled procedure might lead to more practical expertise.

PRIVATE MEMBERS' BILLS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The beginning of a new session brings a score of legislative proposals from the back benches. These are mostly small reforms which M.P.s wish to see made law and have undertaken to sponsor. Sometimes they include highly controversial measures, which are introduced to focus public opinion and induce the Government to show its hand.

Reform of Abortion Law

In the latter category rather than the former falls a Bill, presented on November 21 by Mr. KENNETH ROBINSON (St. Pancras, North, Lab.), entitled Medical Termination of Pregnancy Bill. Its short description describes it as a Bill "to amend the law relating to the termination of pregnancy by registered medical practitioners," and Mr. Robinson has said that its purpose is to bring statute law into line with the judgment in *Rex v. Bourne* in 1939. That judgment, he explained, decided that a doctor was entitled to take into account the risk to the health of a mother, and not merely the immediate risk to her life, by a continued pregnancy. The Bill would prescribe lawful grounds for the termination of a pregnancy by a doctor, with the concurring opinion of another.

Mr. Robinson's desire is to do something to reduce the large number of unskilled illegal abortions. He has got support from both sides of the House for his Bill. The backers are named as Mr. D. Houghton (Lab.), Mr. P. Kirk (Con.), Dr. Barnet Stross (Lab.), Mr. G. Strauss (Lab.), Miss J. Vickers (Con.), Viscount Lambton (Con.), Sir Leslie Plummer (Lab.), Mr. Roy Jenkins (Lab.), Mr. Scholefield Allen, Q.C. (Con.), Mr. J. Parker (Lab.), and Mr. R. W. Sorensen (Lab.).

Passenger Insurance and Protective Headgear

Coming tenth in the ballot, Mr. Robinson lost the opportunity of having his Bill discussed first on one of the half-dozen Fridays available, and it will come up for a second reading on February 10, after the Motor Vehicles (Passenger Insurance) Bill. This measure, presented by Mr. J. CRONIN, another Labour Member, who is a surgeon and trade union adviser on industrial injuries, would make it unlawful for any motor vehicle to be used on the road without there being in force a policy of insurance covering the risk of injury or death to any passenger carried on the vehicle. It, too, has supporters in all parties. By a coincidence, the third Bill for which the day was selected is the Road Safety (Protective Headgear) Bill, intended to

make compulsory the wearing of approved protective headgear by riders and pillion passengers on motor-cycles, scooters, mopeds, and other engine-propelled bicycles. It is sponsored by Lieutenant-Colonel R. G. GROSVENOR, who represents Fermanagh and South Tyrone as a Unionist.

Home Safety

One other of these private Members' measures may be mentioned. This is the Home Safety Bill, which would enable local authorities in England and Wales to promote safety in the home and to make contributions to the activities of voluntary societies engaged in such work. It has been presented by Mr. A. COSTAIN (Folkestone and Hythe, Con.), and is supported, among others, by Dr. Donald Johnson (Carlisle, Con.) and Dr. J. Dickson Mabon (Greenock, Lab.).

QUESTIONS IN THE COMMONS

N.H.S. Reciprocal Arrangements

Mr. ALBERT EVANS (Islington, South-west, Lab.) asked the Minister of Health with which countries he had signed reciprocal agreements for medical treatment. Miss EDITH PITT, Parliamentary Secretary, stated on November 22 that the Government had reciprocal agreements for medical treatment with Denmark, Norway, Sweden, and Yugoslavia, and similar arrangements had been made with the Isle of Man and the Channel Islands (except Sark). Medical treatment was also available for residents on an insurance basis under agreements made with Belgium, France, Israel, Italy, Luxembourg, Malta, and the Netherlands, and, subject to certain limitations, with Australia and Switzerland.

Students from Overseas

Figures supplied by the SECRETARY OF STATE FOR COMMONWEALTH RELATIONS on November 23 of the number of students from Commonwealth countries studying technical or scientific subjects at United Kingdom universities showed that in 1959–60 there were 942 taking medicine and 109 dentistry. They came from these countries: *Australia*, 94 medicine and 11 dentistry; *Canada*, 55 and 2; *Ceylon*, 71 and 11; *Ghana*, 121 and 20; *India*, 161 and 8; *Malaya*, 76 and 8; *New Zealand*, 25 and 4; *Nigeria*, 209 and 18; *Pakistan*, 60 and 0; *South Africa*, 70 and 27.

Similar figures for Colonial territories furnished by the SECRETARY OF STATE FOR THE COLONIES, in which medicine and pharmacy were grouped together, were: *Aden*, 16 medicine, 1 dentistry; *Bahamas*, 4 and 0; *Bermuda*, 1 and 0; *Fiji*, 2 and 0; *Gambia*, 5 and 0; *Gibraltar*, 4 and 0; *Hong Kong*, 94 and 5; *Kenya*, 105 and 5; *Malta*, 12 and 3; *Mauritius*, 54 and 3; *Sarawak*, 3 and 0; *Seychelles*, 2 and 1; *Singapore*, 38 and 4; *Sierra Leone*, 31 and 4; *Tanganyika*, 52 and 0; *Uganda*, 62 and 5; *West Indies*, 193 and 12; and *Zanzibar*, 30 and 0. The totals from Colonial territories are 708 medicine and pharmacy and 43 dentistry. Figures for the *Federation of Rhodesia and Nyasaland*, given separately, showed that there were 33 medical students and one taking dentistry; and from the High Commission Territories two medical students from *Basutoland* and one from *Swaziland*.

1,500 Aliens Sought Treatment

Mr. ALBERT EVANS (Islington, South-west, Lab.) asked for an estimate of the cost of the use of the Health Service by foreign visitors; and what proportion this was of the total cost of the Service. Mr. POWELL said that no reliable estimate could be made, but the proportion must be very small indeed. Mr. EVANS asked what was the number of cases brought to the Minister's notice of foreigners entering, or attempting to enter, this country for the purpose of medical treatment under the Health Service. Mr. POWELL informed him that in 1959, 1,503 aliens were reported as entering, or attempting to enter, this country for medical treatment. Six of these were refused entry. Steps were taken to ensure that the remainder paid for the treatment.

Mr. EVANS asked him to assure the House that he would generally follow the policy of all previous Ministers, and look at the matter not from the narrow nationalistic point of view and refrain from making economies. Mr. POWELL —This thing is an abuse, and however small is the cost of the abuse it should be prevented as far as practicable. There has been no difference of policy in this since the original Act.

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) suggested that effort would be best directed to achieving reciprocity with other countries, and not in tampering with the civilized provisions of the Health Service. Mr. POWELL —It is the provisions of the National Health Service Act in this respect that I am endeavouring to carry out. Mr. MICHAEL FOOT (Ebbw Vale, Lab.) said that when the Health Service was first introduced the idea of giving service to foreigners was not regarded as an abuse; they gloried in it. The Minister would sustain the traditions of the House better if he repudiated the advice of his friends to undermine this service. Mr. POWELL—There has never been any question of people from abroad who fall ill here receiving attention under the Health Service. What is in question, and what is not in accordance with the Act, is that aliens should come here for the purpose of getting treatment under the Act.

Mental Hospital Inquiry

Mr. ERIC FLETCHER (Islington, East, Lab.) asked the Minister whether he had investigated the circumstances in which Alan Smith, a boy of 12 years of age, who was kept in a ward at St. Lawrence's Hospital, Caterham, for six months with 58 mentally defective men, many of whom were deformed, was subjected to indecent assaults. Mr. POWELL: A committee of inquiry set up by the South-West Metropolitan Regional Hospital Board has investigated this allegation and found it to be not substantiated.*

Mr. FLETCHER asked for an assurance that in future children of 12 would not be put in mental hospitals with a number of mentally defective adults. Mr. POWELL: Not necessarily. The committee of inquiry addressed their minds to the point, and were satisfied beyond all reasonable doubt that the decision to transfer the boy to the ward in question was correct.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) asked if these conditions obtained in other hospitals. This might be an exceptional case, but if these nineteenth-century conditions were accepted other children might be put with men in this condition. Mr. POWELL replied that in the country at large about 700 mentally subnormal children were accommodated in adult wards. In many cases the nature both of the children concerned and of the other patients in the ward was such that that might be the best accommodation. He added that they looked forward to great improvements in mental hospital accommodation in the coming years, and that would no doubt reduce the number, but the figures in themselves were not necessarily evidence that the children were inadequately cared for.

*See *Brit. med. J.*, November 12, p. 1459.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in October was 70, compared with 90 in the previous month and 91 in October, 1959.

The number of cases of industrial disease in the United Kingdom reported during October were as follows: aniline

poisoning 3, epitheliomatous ulceration 19, chrome ulceration 33, total 55. There were no deaths.—*Ministry of Labour Gazette*, November, 1960.

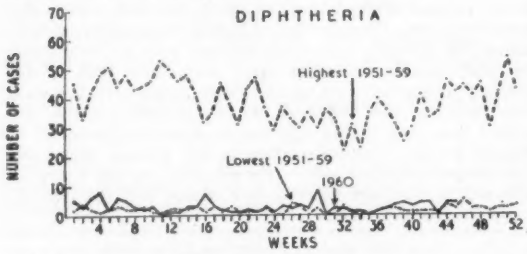
Infectious Diseases

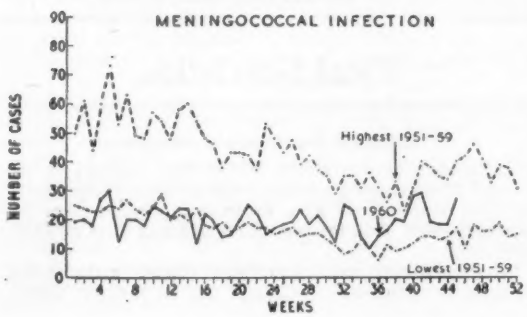
Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Nov. 12	Nov. 19
Dysentery		
London	40	72
Chelsea	0	18
Nottinghamshire	25	57
Carlton U.D.	14	20
Bingham R.D.	9	25
Somersetshire	0	15
Langport R.D.	0	15
Yorkshire West Riding	90	72
Leeds C.B.	41	25
Todmorden M.B.	4	14
Glasgow	122	102
Measles		
Lancashire	1,553	1,590
Burnley C.B.	93	106
Liverpool C.B.	200	221
Manchester C.B.	90	144
Oldham C.B.	176	165
Yorkshire West Riding	453	624
Bradford C.B.	71	163
Acute poliomyelitis		
London	0	4
Food-poisoning		
London	17	41
Westminster	1	10
Glasgow	9	34

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 12** (No. 45) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	4	1	2	0		8	7	3	0	2
Dysentery	443	40	164	5	6	538	59	237	6	2
Encephalitis, acute	3	0		0		5	0		0	
Enteric fever:										
Typhoid	2	2	0	0		8	5	0	0	13
Paratyphoid	4	0	0	0		4	1	0	0	1(B)
Food-poisoning	210	17	11	3		147	16	14	0	
Infective enteritis or diarrhoea under 2 years				10	40				8	31
Measles*	4,868	301	116	12	77	1,071	19	12	13	133
Meningococcal infection	27	5	5	0	2	17	2	5	0	
Ophthalmia neonatorum	17	2	3	0		19	2	16	0	
Pneumonia†	232	18	135	2	2	180	15	151	4	
Poliomyelitis, acute:										
Paralytic	8	0	0	0	2	21	7	0	1	1
Non-paralytic	0	0	1			3	0	0		
Puerperal fever§	174	32	12	1		223	37	21	1	
Scarlet fever	435	23	67	33	16	1,059	54	156	23	34
Tuberculosis:										
Respiratory	348	58	69	13		370	38	77	12	
Non-respiratory	45	6	10	4		55	6	7	1	
Whooping-cough	835	69	83	2	45	641	49	136	8	110

DEATHS	1960 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	1959 Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	2	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	1	0	1	1	6	0	3	1	0
Influenza	12	1	0	0	2	22	0	0	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	510	46	15	13	7	476	54	14	13	8
Poliomyelitis, acute	1	0		0	0	1	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	62	5	5	0	3	74	8	6	0	2
Non-respiratory		0	1	0	0		1	1	0	0
Whooping-cough	1	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	331	37	37	18	5	260	29	19	13	9
Deaths (excluding stillbirths)	10,255	822	569	138	171	9,902	830	561	129	148
LIVE BIRTHS	14,584	1294	961	288	330	12,926	1090	835	224	352
STILLBIRTHS	270	20	20			282	16	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Vaccination Against Poliomyelitis

The MINISTER OF HEALTH announces that there is enough poliomyelitis vaccine to permit vaccination from January 1 of those aged 40 and over who are not covered by the existing arrangements.

Medical Research Council's New Chairman

Viscount AMORY is to succeed the Earl of LIMERICK as chairman of the Medical Research Council from December 1. Viscount Amory, formerly Mr. Heathcoat Amory, was Chancellor of the Exchequer from January, 1958, until his resignation in July of this year.

A.M.A. Opposes Mr. Kennedy's Plan

According to the *New York Times* (November 28) the American Medical Association has "served notice" on President-elect JOHN F. KENNEDY that it would marshal its "tremendous strength" in an effort to kill his proposed programme of medical care for the aged. Delegates to the A.M.A.'s fourteenth annual clinical meeting in Washington on November 27 were urged by Dr. E. B. HOWARD, assistant executive vice-president, to stand fast in opposition to Mr. Kennedy's plan to tie medical care for the aged to the social security system.

Chair of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine

Dr. D. G. EVANS, M.Sc., Ph.D., F.R.S., director of the department of biological standards of the National Institute for Medical Research, has been appointed to the University chair of bacteriology and immunology at the London School of Hygiene and Tropical Medicine. He succeeds Professor E. T. C. SPOONER, who has become Dean of the School.

Dr. Evans graduated in science at the University of Manchester in 1933, and in 1934 joined the department of bacteriology there, where he obtained his Ph.D. degree. At the beginning of the war he became a member of the research staff of the National Institute for Medical Research and worked with Sir PERCIVAL HARTLEY in the department of biological standards. He returned to Manchester in 1947 as reader in the department of bacteriology, and was awarded the degree of D.Sc. in 1948. In 1955 he was appointed head of the biological standards control laboratory at Hampstead and in 1958 became director of the department of biological standards, in which the control laboratory is incorporated. He was elected to the Fellowship of the Royal Society in 1960. Since 1934 Dr. Evans has been actively engaged in research, mainly on the pathogenesis and prophylaxis of whooping-cough and anaerobic wound infections, and in the field of biological standardization. Since his appointment as head of the control laboratory in 1955 he has been mainly concerned with building up a laboratory to deal primarily with the control of poliomyelitis vaccine in this country. He is a member of a number of Medical Research Council committees, of the British Pharmacopoeia Commission, and of the panel of the Expert Committee on Biological Standardization of the World Health Organization; he has also served on various other W.H.O. committees.

Chair of Psychiatry, Middlesex Hospital Medical School

Dr. J. D. N. HILL, senior lecturer at the Institute of Psychiatry and lecturer in psychological medicine at King's College Hospital Medical School, has been appointed to the newly created London University chair of psychiatry tenable at Middlesex Hospital Medical School.

Dr. Hill, who is 47, was educated at Shrewsbury School and St. Thomas's Hospital, where he qualified M.R.C.S., L.R.C.P. in 1936, followed by the M.B., B.S. (London) in 1937. He was chief assistant in the department of psychological medicine at St. Thomas's before joining the Maudsley Hospital staff in 1938. He obtained the D.P.M. (London) in 1940 and the M.R.C.P. (London) in the same year, being elected F.R.C.P. in 1949. Throughout the war he worked at Sutton Emergency Hospital, and in 1941 was awarded, jointly with the late Professor ALEXANDER KENNEDY, the Gaskell Gold Medal of the Royal Medico-Psychological Association. Since the war, in addition to his present posts, he has been consultant in electroencephalography at the National Hospital, Queen Square. His subsidiary posts since the war have included appointments as consultant psychiatrist for a period of three years to Queen Charlotte's Hospital and consultant in electroencephalography to the South-east Metropolitan Region. As part of his appointment at the Institute of Psychiatry, he has held an honorary consultant appointment to the Maudsley–Bethlem Hospital and has worked there mainly on the problems of epilepsy associated with mental disorder. Much of his research and publications has been concerned with this field and in particular with temporal lobe epilepsy. He has contributed chapters on either psychiatry or electroencephalography to about 15 textbooks, in particular the chapter on psychiatry in Sir John Richardson's *Practice of Medicine*, and was joint editor of the only British textbook on electroencephalography, published in 1950. He was a member of the Medical Research Council and Clinical Research Board from 1956 to 1960 and is a member of the Central Health Services Council and the Standing Medical Advisory Committee to the Ministry of Health. He served recently on the working party appointed by the Minister to advise on the function of the special hospitals (Broadmoor, Moss Side, and Rampton) in the light of the changes of the law consequent upon the new Mental Health Act.

Chair of Obstetrics and Gynaecology, St. Mary's Hospital Medical School

Dr. I. MACGILLIVRAY, senior lecturer in the University of Aberdeen and consultant obstetrician and gynaecologist at the Aberdeen Royal Infirmary and Aberdeen Maternity Hospital, has been appointed to the London University Chair of Obstetrics and Gynaecology tenable at St. Mary's Hospital Medical School.

After graduating M.B., Ch.B. at Glasgow University in 1944 Dr. MacGillivray held a house-surgeon post at Falkirk, and thereafter served for two years on a troopship in the Far East. On his return he held resident posts in Falkirk and Glasgow. In 1948 he was awarded a University research scholarship in the research department of the Glasgow Royal Maternity Hospital. He became M.R.C.O.G. in 1949 and was appointed University lecturer in midwifery in 1950. In 1953 he proceeded M.D., and in the same year he was appointed senior lecturer in obstetrics and gynaecology at the University of Bristol. He moved to his present post in Aberdeen in 1955 with an honorary appointment in the Medical Research Council's Obstetric Medicine Research Unit. He was elected F.R.C.O.G. in 1959, and gave the Blair Bell Memorial Lecture at the Royal College of Obstetricians and Gynaecologists in 1960. His major research contributions have been epidemiological, and fluid and electrolyte studies in pre-eclamptic toxaemia.

Chair of Psychological Medicine, Edinburgh University

Dr. G. M. CARSTAIRS, director of the Medical Research Council Unit for Research on the Epidemiology of Psychiatric Illness, has been appointed to the chair of psychological medicine in the University of Edinburgh in succession to the late Professor ALEXANDER KENNEDY.

Dr. Carstairs, who is 45 years of age, was born in India, where his father was a Church of Scotland missionary. He was educated at George Watson's College and Edinburgh University, where he read arts as well as medicine, being medallist in Fine Art. He showed prowess as a runner at both school and university, was Scottish champion for the three miles in 1937 to 1939, and several times ran for Scotland and Great Britain in international matches. In 1941 he graduated M.B., Ch.B., and after house-physician posts he served for four and a half years as a medical officer in the Royal Air Force in Europe and the Far East, where he learned to fly. After the war Dr. Carstairs held appointments at mental hospitals in Edinburgh and Oxford, when he was admitted M.R.C.P.Ed. and took the London University D.P.M. While registrar at Warneford Hospital, Oxford, he studied social anthropology as an external student of the Institute of Social

[Teddy Schwarz

Anthropology. For the next four years he held research fellowships which took him first to New York as a Commonwealth Fund Fellow, where he studied social anthropology under Dr. MARGARET MEAD during 1948 and 1949, and then to Rajputana for two years, where he carried out research while living in three primitive village communities. During part of this time he held a Rockefeller Grant and a Fellowship from the Henderson Trust and worked as a graduate student of Cambridge under the direction of Professor MEYER FORTES. His researches in Rajputana are published in his book, *The Twice Born*. Since 1953 Dr. Carstairs has been engaged in psychiatric research and practice at Maudsley Hospital, London. He took up his present post in April, 1960. Dr. Carstairs is a descendant of William Carstares, principal of Edinburgh University from 1703 to 1716.

Governor of Eastern Nigeria

Sir FRANCIS IBIAM, a medical missionary with the Church of Scotland Mission, Calabar, Nigeria, since 1936, and principal of the Hope Waddell Training Institute, Calabar, since 1957, has been appointed governor of Eastern Nigeria.

Sir Francis, who was born in 1906, was educated at the Institute of which he is now principal, at King's College, Lagos, and at the University of St. Andrews, Scotland, where he graduated M.B., Ch.B. in 1934. He started and built up a new hospital at Abiriba under the Calabar Mission from 1936 to 1945, and was medical superintendent of the C.S.M. Hospital at Itu from 1945 to 1948. He was closely concerned with politics from 1947 to 1953, and took part in the conferences on the political future of the country in 1949. He retired from politics after the Eastern Nigerian political crisis in 1953, and holds many appointments in the medical, educational, and missionary fields. He has been president of the Christian Council of Nigeria since 1955, and chairman of the Council of University College, Ibadan, since 1958. He was appointed K.B.E. in 1951 in recognition of his services to Nigeria.

[*David Peters*

Anglo-French Medical Exchange Bursaries

Applications are now invited for these awards, offered by the Institut National d'Hygiène, and tenable at any hospital or research institute in France. Awards are normally made for periods of between two and four months. The value of the bursary is 870 N.F. (about £63) per month, tax free. In addition, each bursar receives a grant of £15 towards his travelling expenses. Information about work in progress in France can be obtained from the Scientific Office, French Embassy, 22 Wilton Crescent, London S.W.1. Requests for application forms should be sent to the Director, The Ciba Foundation, 41 Portland Place, London W.1. The closing date for applications is January 31, 1961.

Edgar-Gentilli Scholarship

The Royal College of Obstetricians and Gynaecologists invites applications for the Edgar-Gentilli Scholarship (valued at up to £1,000 a year and tenable for one year in the first place), the primary object of which is to encourage research, either in the United Kingdom or overseas, into the causes, nature, and treatment of chorion epithelioma. Any work, however, which is concerned with the structure, function, and behaviour of the trophoblast, with the interaction of the trophoblast and maternal tissue, or with the normal or diseased placenta will be regarded as having a bearing on this problem. Details may be obtained from the Secretary of the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London N.W.1. The closing date for applications is December 31.

International Cultural Exchange

A four-week medical, social, and cultural tour of Pakistan and India is being arranged from September 1, 1961, with the aim of increasing friendship and understanding between the countries concerned. Similar visits were arranged in 1950, 1951, and 1955, when those who were taking part stayed with local families, attended congresses, and were taken on sightseeing tours. The normal air fare is halved by chartering a special 'plane. Doctors who would like further details should write to Mr. R. U. HINGORANI, 128 Harley Street, London W.1.

People in the News

Sir ROBERT PLATT, P.R.C.P., has been elected to an Honorary Fellowship of the American College of Physicians. This will be conferred when he visits the United States in May to give the Lilly Lecture.

Dr. G. R. GRAHAM has been appointed consultant clinical physiologist to the Hospital for Sick Children, Great Ormond Street, one of the few posts of its kind in the Health Service.

Dr. D. L. EASTY, who is 27, has been appointed medical officer to the Falkland Islands Dependencies Survey which sailed for the Antarctic on December 2 in the *Kista Dan*.

COMING EVENTS

Rickman Godlee Lecture.—Sir SOLLY ZUCKERMAN, F.R.S., "The Social Function of Science—1960," December 8, 5.30 p.m., Anatomy Theatre, University College London, Gower Street, London W.C.1. Admission free without ticket.

British Medical Association.—Lecture-discussion, "Fractures Around the Wrist," opened by Mr. H. OSMOND-CLARKE, December 15, 5.30 p.m. (tea, 5 p.m.), B.M.A. House, Tavistock Square, London W.C.1. Chairman: Mr. H. H. LANGSTON. Open to all medical practitioners and students.

Faculty of Radiologists.—Joint meeting with British Institute of Radiology and Royal Society of Medicine Section of Radiology, December 16, 4.30 p.m., Royal Society of Medicine, 1 Wimpole Street, London W.1: "Diseases of the Liver"; December 17, 10 a.m., Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2: "Tumours of the Mandible."

"Treatment of Primary Arterial Hypertension."—Symposium, December 17, 18, Milan. Details from Professor W. MONTORSI, Accademia Lombarda, 3 Via Festa del Perdono, Milan, Italy.

Glasgow University and R.F.P.S. Postgraduate Medical Education Committee.—Clinical teaching ward rounds for postgraduate students from January 12. See advertisement p. 72 for details.

Family Planning Association.—Training course for medical practitioners in London in January. For details see advertisement p. 73.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

JOURNAL OF CLINICAL PATHOLOGY

The Assay and Properties of Labile Factor (Factor V). Armand J. Quick.
The Buccal Mucosa in Anaemia. Allan Jacobs.
A Rapid "Side-room" Method for the Determination of Plasma Fibrinogen Concentration as Fibrin. G. I. C. Ingram and Myrtle O. Matchett.
Diagnostic Difficulties in Mild Haemophilia and Christmas Disease. Barbara M Fessey, M. J. Meynell, and W. T. Cooke.
Serum Haptoglobins in Haemolytic States. J. A. Owen, G. C. de Gruchy, and H. Smith.
Multiple Primary Cancers: Primary Malignant Lymphomas and Carcinomas of the Intestinal Tract in the Same Patient. John S. Cornes.
The Weights of Kidneys in Late Intra-uterine Life and Childhood. John L. Emery and Avinash Mithal.
Parathyroid Adenoma with Misleading Phosphate Excretion Tests. H. G. Morgan, W K. Stewart, and J. Grieve.
The Relation of Thyroid Auto-immunity to Round-celled Infiltration of the Thyroid Gland. R. O. K. Schade, S. G. Owen, G. A. Smart, and R. Hall.
The Relation of Serum Uric Acid to Haemoglobin Level in Patients with Cardiac and Respiratory Disease. J. G Lewis and J. E. Gardner.
The Determination of Magnesium in Biological Fluids and Tissues by Flame Spectrophotometry. Nancy Alcock, I. MacIntyre, and Ingeborg Radde
Serum Proteins and Blood Alpha Amino Nitrogen in Cerebral Palsy. David Burman and R. R. Rembolt.
A Comparison of Calculated and Estimated Osmolarities of Urine. M. H. Roscoe.
The Urinary Excretion of 5-Hydroxyindoleacetic Acid in Patients with Menopausal Flushing. N. R Rowell and Jean W. Summerscales.
The Isolation and Identification of Haemophilus spp. from Unusual Lesions in Children. K. B. Rogers, K. Zinnemann, and W. P. Foster.
Technical Methods.
Association of Clinical Pathologists: 65th General Meeting.
Nomenclature of Abnormal Haemoglobins.
Index.

Volume 13, No. 6. (Bi-monthly; £4 4s. annually.)

BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE

Obstetric and Social Origins of Mentally Handicapped Children. D. V. I. Fairweather and R. Illsley.
Health Hazards of Cigarette Smoking. Current Popular Beliefs. A. Cartwright, F. M. Martin, and J. G. Thomson.
Asian Influenza in Pregnancy and Congenital Defects. R. Doll, A. Bradford Hill, and J. Sakula.
Pilot Experiment in the Rehabilitation of Long-hospitalized Male Schizophrenic Patients. J. K. Wing.
Demographic Approach to the Problem of the Connexion between Lung Cancer and Smoking. J. R. Rele.
Infant and Early Childhood Death Rates over the Last Hundred Years in the Negro Population of Antigua, British West Indies. K. H. Uttley.
Diet and Serum Protein Levels of Urban Zulu Adults. J. H. Abramson, B. Gampel, N. Scotch, and C. Slome.
Index.

Volume 14, No. 4. (Quarterly; £3 annually.)

JOURNAL OF NEUROLOGY, NEUROSURGERY, AND PSYCHIATRY

Nerve Fibre Degeneration in the Brain in Amyotrophic Lateral Sclerosis. Marion C. Smith.
The Distribution of Lewy Bodies in the Central and Autonomic Nervous Systems in Idiopathic Paralysis Agitans. W. A. den Hartog Jager and J. Bethlem.
The Effect of Haemodialysis in Myasthenia Gravis. Ernst Stricker, Heinrich Thölen, Marie-Agnes Massini, and Hans Staub.
Traumatic Epilepsy after Closed Head Injuries. W. Bryan Jennett and Walpole Lewin.
A Myopathy Presenting in Adult Life with Features Suggestive of Glycogen Storage Disease. J. MacDonald Holmes, C. R. Houghton, and A. L. Woolf.
Changes in Nerve Conduction with Ulnar Lesions at the Elbow. R. W. Gilliatt and P. K. Thomas.
The Clinical Significance of the Sino-vertebral Nerve of the Cervical Spine in Relation to the Cervical Disk Syndrome. Ralph B. Cloward.
An Experimental Analysis of Confabulation in a Case of Korsakoff's Syndrome Using a Tachistoscopic Method. Maria Wyke and Elizabeth Warrington.
The Effect of Focal Lesions of the Brain upon Auditory and Visual Recent Memory in Man. Lucjan Stepień and Stanisław Sierpiński.
5-Hydroxyindoles in Mental Deficiency. C. M. B. Pare, M. Sandler, and R. S. Stacey.
Society of British Neurological Surgeons: 61st Meeting.
Book Reviews.
Index.

Volume 23, No. 4. (Quarterly; £3 annually.)

BRITISH HEART JOURNAL

The Effects of Sodium Antimony Tartrate on the Myocardium. M. Honey.
The Atrial Electrocardiogram as a Guide to Prognosis after Mitral Valvotomy. Patrick Mounsey.
Electrocardiographic and Radiological Studies in Hiatus Hernia. J. B. McGuinness and S. D. Scott Park.
The Influence of Meteorological Changes on Coronary Thrombosis. A. O. Adesola.
Electrocardiographic Changes in Hypothermia. N. A. Wynne, J. A. Fuller, and P. Szekely.
The Effects of Digitalis on the Hypothermic Heart. P. Szekely and N. A. Wynne.
Acute Non-specific Pericarditis. W. G. A. Swan.
Spontaneous Rupture of the Heart. Arnold Levene.
The Electrocardiogram of the Mountaineer at High Altitude. Frederic Jackson and Hywel Davies.
Combined Congenital Subaortic Stenosis and Infundibular Pulmonary Stenosis. H. N. Neufeld, P. A. Ongley, and J. E. Edward.
Atrial Flutter with Complete Heart Block. C. P. Newcombe, D. De Souza, and J. R. H. Towers.
The Small Pulmonary Arteries Studied by a New Injection Method. W. R. L. James, G. M. Owen, and A. J. Thomas.
Cine-angiocardiographic Studies of the Outflow Tract in Isolated Pulmonary Valvular Stenosis. H. Watson, C. Pickard, K. G. Lowe, and I. G. W. Hill.
Unusual Forms of Heart Block in Infancy. A. Castellanos, Jr., H. De La Torre, L. Azán, and J. M. Calviño.
Diagnosis of Pulmonary Regurgitation by a Dye Method. S. H. Wanzer, L. Cudkowicz, and R. Daley.
Complete Heart Block Treated with Corticotrophin and Corticosteroid. C. P. Aber and E. Wyn Jones.
Case Reports.
Index.

Volume 22, No. 5. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, December 5

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. F. Goodwin: Effects of Drugs on the Pulmonary Circulation.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. D. M. Green: Auto-immune Disease of the Thyroid.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Professor W. Feldberg, F.R.S.: Mediators of Allergic Reactions.

Tuesday, December 6

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor D. G. Catcheside: Functional Structure of Genes.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 3 p.m., Mr. J. A. Stallworthy: Carcinoma of the Uterus.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Eliot Slater: The Schizophrenic-like Psychoses of Epilepsy.
RESEARCH DEFENCE SOCIETY.—At Physiology Lecture Theatre, University College, London, 5.30 p.m., Stephen Paget Memorial Lecture by Professor J. H. Burn, F.R.S.: Testing Drugs on Man. Followed by annual general meeting of society.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Professor F. A. R. Stammers: Pain in the Arm.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Mr. Aleck Bourne: Some of My Mistakes.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. K. I. Nissen: Orthopaedic Surgery of Spastic States.

Wednesday, December 7

BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTION.—At 36 Harborne Road, Edgbaston, 8.30 p.m., Dr. R. Bodley Scott: Acute Leukaemia—Present Therapeutic Position.
CHILTERN MEDICAL SOCIETY.—At Beechtree Hotel, Beaconsfield, 8 for 8.30 p.m., illustrated talk by Mr. J. P. Reidy: Russian Reconnaissance.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Yeasts as Pathogens.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. M. Paneth: Surgery of Secundum Defects of the Atrial Septum.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 2 p.m., Mr. G. B. Gibson: Post-maturity.
PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.—At 17 Bloomsbury Square, London W.C., 7.30 p.m., Mr. G. R. A. Short, F.P.S., F.L.S.: Flavours and Colours in Medicine.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. A. E. Kellie: Steroid Assays.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—2.30 p.m., Bradshaw Lecture by Sir Stanford Cade: Malignant Melanoma.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. Kenneth Soddy: World Mental Health Year—International Trends in Mental Health Work.
ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Dr. K. G. Lowe: Renal Tubular Function.

Thursday, December 8

ALFRED ADLER MEDICAL SOCIETY.—At 11 Chandos Street, London W., 8 p.m., Dr. W. Barlow: Anxiety and Muscle Tension.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. E. J. L. Lowbury: Drug Resistance and the Response to Chemotherapy.
FOUNTAIN HOSPITAL.—5.30 p.m., (1) Dr. M. Sandler: 5-Hydroxyindoles and Brain Function; (2) Dr. L. Sinclair: Aminoacids, Brain Function, and Epilepsy. A discussion will follow.
HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor M. L. Rosenheim: The Small Kidney.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. F. Borrie: Disorders of Function in Cutaneous Blood Vessels and Lymphatics.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Miss J. A. M. Moore: Dysmenorrhoea.
LIVERPOOL MEDICAL INSTITUTION.—Mr. W. Kulke: The Application of Radioisotopes to Medical Conditions excluding Thyroid Disease; Mr. Donald Young: A New Technique of Repair of Epigastric Incisional Hernia.
LONDON UNIVERSITY.—At Royal Dental Hospital of London School of Dental Surgery, 5.30 p.m., Professor James T. Irving (Harvard University): A Comparison of Calcification Mechanisms in Bone and Teeth.
ROYAL ARMY MEDICAL COLLEGE.—At Royal Society of Tropical Medicine and Hygiene, 7.30 p.m., Symposium on Hookworm Disease. Speakers: Dr. H. Foy, Dr. G. Stott, and Dr. E. Van Oye.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Robert Jones Lecture by Mr. H. J. Seddon: Manchester Ship Canal and the Colonial Frontier.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Hamilton Paterson: postgraduate demonstration in neurology.
UNIVERSITY COLLEGE LONDON AND UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL.—At Anatomy Theatre, University College London, Gower Street, W.C., 5.30 p.m., Rickman Godlee Lecture by Sir Solly Zuckerman, F.R.S.: Social Function of Science—1960.

Friday, December 9

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. Brian Russell: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Dr. Norman Hulbert: Headache and Facial Pain.
PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., Joint discussion meeting with Plymouth Section, B.D.A. Subject: Mutual Problems.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Dr. Victor Wynn: Metabolic Care of the Surgical Patient. (2) 4 p.m., Dr. J Badenoch: Malabsorption Syndromes.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: WELSH BRANCH.—At B.M.A. House, 195 Newport Road, Cardiff, 6.30 p.m., Dr. Melvyn Howe: Geographical Distribution of Disease Mortality in Wales.

Saturday, December 10

SHEFFIELD REGIONAL PSYCHIATRIC ASSOCIATION.—At Mapperley Hospital, Nottingham, 2.30 p.m., Dr. E. Stengel: Relationship Between Psychiatric Classification, Nomenclature, and Diagnosis.

Sunday, December 11

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE.—At Theatre 1, Clinical Sciences Building, York Place, Manchester, 11 a.m., in conjunction with North-west England Faculty, College of General Practitioners. Mr. A. R. Anscombe: Surgical Aspects of Jaundice.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Myles.—On October 9, 1960, to Barbara (formerly Holmes), M.B., B.Ch., D.A., and John G. B. Myles, M.B., F.R.C.S., a daughter—Carolyne Anne Boulton.

DEATHS

Fox.—On November 10, 1960, at Chota Ghur, Little Clacton, Essex, Charles Joshua Fox, T.D., M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., T.A.R.O., retired.
Hockin.—On November 9, 1960, in hospital, Janette Avril Hockin, M.B., Ch.B., aged 28.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Serum After Toxoid

Q.—*Is there more danger of precipitating anaphylactic shock by injecting tetanus antitoxin in a child who has had normal inoculations against whooping-cough, diphtheria, tetanus, and poliomyelitis than in a child who has not received tetanus toxoid protection?*

A.—The fact that a child has been given tetanus toxoid is no reason for supposing that a subsequent injection of tetanus antitoxin will precipitate anaphylactic shock. The toxoid is the detoxicated (formalin-treated) toxin of the tetanus bacillus and contains no serum, whereas the antitoxin is the serum of a horse immunized against tetanus. The toxoid contains no component which can sensitize the subject in such a way that an allergic reaction will follow the subsequent administration of horse serum. Any antitoxic serum prepared in the horse, even when properly refined, may give rise to allergic symptoms, but these would not be aggravated by the fact that tetanus toxoid had previously been administered. The only prophylactic now in common use which contains horse serum is diphtheria vaccine, T.A.F.; the small amount of serum in this preparation has been known occasionally to cause sensitization, but this has been manifested by "accelerated" serum sickness rather than by anaphylaxis. Since repeated injections of tetanus antitoxin (or any other serum) are undesirable, the modern emphasis is rightly on establishing active immunity and maintaining it with properly spaced reinforcing doses.

Pyelography and Kidney Function

Q.—*Does failure, after 90 minutes, to visualize a kidney with intravenous pyelography (excretion from other kidney normal) mean that it is permanently functionless?*

A.—Failure after ninety minutes to visualize a kidney with intravenous pyelography does not mean that it is permanently functionless. After an attack of renal colic pyelography may show no function for four hours. If the examination is continued, a good pyelogram may be obtained twelve hours later.

Contamination or Infection

Q.—*If centrifugalized urine on repeated examinations is found to be devoid of pus cells and a catheterized sample on culture is found to contain B. coli, how could it be interpreted—contamination or infection? How can contamination be differentiated from real infection?*

A.—If numerous bacilli were present in the deposits of the mid-stream specimen of urine, and *B. coli* were subsequently cultured in great numbers from a catheter specimen of urine, then the correct interpretation would appear to be that of a genuine bacteriuria. If, on the other hand, no great numbers of bacilli were seen in the centrifuged deposits of the mid-stream urine and catheter specimens of urine, the growth obtained would be regarded as "probably contaminant." Repeated examination of catheter specimens of urine might help to confirm the diagnosis of bacteriuria. The simplest definition of bacteriuria is that of continuous or intermittent excretion of bacteria in the urine without any gross signs of inflammation, leaving open the relationship between bacteriuria and inflammation, which can be decided only by considering all clinical and laboratory findings in each case.

The second question, on the differentiation of contamination from real infection, is somewhat easier to answer. Provided a catheter specimen of urine is reasonably fresh a number of pus cells will always be present in infection. Difficulties of interpretation may arise when the specimen has been collected more than 8–10 hours previously, since pus cells may no longer be recognizable and the number of bacteria may be increased. A rough estimation of the number of pus cells present and of the growth obtained is also helpful, since "scanty pus cells and growth" is normally taken as indicative of contamination, both in mid-stream and catheter specimens, and even more so in a female than in a male. The bacteriologist finds it hard to decide, however, whether moderate numbers of pus cells together with scanty or moderate growth in a mid-stream specimen of urine signify infection or not. Examination of a subsequent catheter specimen would help with the interpretation.

Some rare cases may arise in which the principles outlined above do not apply. Thus, in a case of agranulocytosis severe urinary-tract infection was the predominant symptom; the absence of a cellular reaction in this case led to the wrong deduction of "contaminated urine."

NOTES AND COMMENTS

Intervals between Polio Injections.—Dr. I. A. MACDOUGALL (Winchester) writes: I was interested to read ("Any Questions?" August 27, p. 678) that the maximum recommended interval between the first and second injections should be six weeks. In many rural areas local authority child welfare clinics are held only at monthly intervals, and it is not uncommon for a child or mother, having had one injection, to miss the next clinic and thus allow at least eight weeks to elapse before attending again. In such clinics it has been the practice to allow the second injection to be given up to a three-month interval. In the early days of the scheme vaccine was not always readily available and there were, in consequence, certain administrative difficulties which quite often resulted in the spacing of the first two injections being over six weeks. May I please have comments on this procedure?

OUR EXPERT replies: The interval of six weeks between the first and second injections of polio vaccine is recommended because it is *thought* by immunological experts that this is the interval most likely to result in the best response to the secondary stimulus of the second dose. In fact, it is not *known* that this is the best interval, because not enough work has been done to prove it. For example, it has been shown that three doses of polio vaccine (given between the ages of 7 and 10 months) were better than two doses, but it is not at present clear whether this was actually because there were three doses or whether it was because the first and third doses were spaced eight weeks apart. From a limited amount of evidence, however, it has been *deduced* that the best time to follow the initial basal immunity with a second dose of antigen which will provide the best possible stimulus to the immunity-producing mechanism, so far as we understand it, is six weeks. My opinion is that, if for administrative and domestic reasons an interval of eight weeks is more convenient, it would do little harm to adopt this interval. An interval of three months may very well be quite satisfactory in many cases (there is a considerable degree of individual variation), but should be avoided, so far as possible, in favour of an interval of six or eight weeks.

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